The asymmetric reduction of ketones

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The Asymmetric Reduction of Ketones.

Submitted by John Richard Studley,

for the degree of Ph.D.

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Contents.

This report is dedicated to my parents for their love and support.

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Glossary of Terms.

Anti-emetic	An agent that suppresses vomiting. Used to treat such conditions as motion sickness and vertigo and to counteract nausea and vomiting caused by other drugs.
Asymmetric	Non symmetric.
Chiral	An object which is not superimposable upon it's mirror image.
Chiral Centre	An atom, and groups around it, which is not superimposable upon it's mirror image.
Chirality	The general property of "handedness".
Diastereoisomer	Two compounds which are stereoisomers but not enantiomers have a diastereomeric relationship.
Diastereomeric Excess	% d.e. = ([A]-[B]/[A]+[B]) x 100 (expressed as % d.e.) where A and B are the amounts of individual diastereoisomers produced.
Diastereoselective	Any reaction in which only one diastereoisomer is formed exclusively or predominantly.
Diastereotopic	Replacement of an atom or group (one of a pair of identical groups) with a third group (unlike any existing group) gives rise to diastereoisomers.
Enantiomer	Many compounds may be obtained in two different forms in which the molecular structures are constitutionally identical but differ in the three-dimensional arrangement of atoms such that they are related as mirror images. In such a case the two possible forms are called enantiomers.
Enantiomeric Excess	% e.e. = ([A]-[B]/[A]+[B]) x 100 (expressed as % e.e.) where A and B are the amounts of individual enantiomers produced.
Enantioselective	Any reaction in which only one enantiomer is formed exclusively or predominantly.
Enantiotopic	Two atoms or groups that upon replacement with a third group (unlike any existing group) gives rise to an enantiomer.
Epimers	Two diastereoisomers that have a different configuration at only one chiral centre.
Homochiral	A compound which is diastereomerically and enantiomerically pure.
Prochiral	A compound or group that has two enantiotopic atoms or groups.

Racemic	Consisting of a 1:1 mixture of enantiomers.
Re-face	The face of a double bond in which the three groups, arranged by the priority rules, have the order A>B>C, in a clockwise fashion.
Si-face	The face of a double bond in which the three groups, arranged by the priority rules, have the order A>B>C, in an anti-clockwise fashion.
Stereocentre	See chiral centre.
Stereogenic	See chiral centre.

Abbreviations.

Δ.....heat.

δ..... *Spec.* chemical shift (given parts per million / ppm).

Å..... angstrom.

aq..... aqueous.

Ar..... aryl.

BMS..... borane dimethyl sulfide complex.

t-BOC..... *tert*-butoxycarbonyl.

Bn..... benzyl.

n-Bu..... straight chain butyl ($CH_3(CH_2)_3$-).

t-Bu..... *tert*-butyl ($[CH_3]_3C$-).

t-BDMS.... *tert*-butyldimethylsilyl.

t-BDPS..... *tert*-butyldiphenylsilyl.

bp..... boiling point.

br..... *Spec.* broad.

ca..... *circa* (*Lat.* about).

CI..... chemical ionisation.

d..... *Spec.* doublet.

DCC..... N, N'-dicyclohexyl carbodiimide.

DCM..... dichloromethane.

DCU..... N, N'-dicyclohexyl urea

d.e..... diastereomeric excess.

DMAP..... 4-N, N'-dimethylamino pyridine.

E^+..... electrophile.

e.e..... enantiomeric excess.

EI..... electron ionisation.

Et..... ethyl (CH_3CH_2-).

eq..... equivalents.

HPLC..... high performance liquid chromatography.

hr..... hour.

Hz..... hertz.

IR..... infra red.

J..... *Spec.* coupling constant (given in Hertz / Hz).

LDA..... lithium diisopropylamide.

M^+..... molecular ion.

Me..... methyl (CH_3-).

min..... minutes.

m.p..... melting point.

MTPA..... α-methoxy-α-(trifluo-methyl)-phenylacetic acid (Moshers acid).

NMR..... *Spec.* nuclear magnetic resonance spectroscopy.

Nu..... nucleophile.

o-..... *ortho.* (1, 2-substituted benzene.

p-..... *para.* (1, 4-substituted benzene.

p..... *Spec.* pentet.

PDC..... pyridinium dichromate.

Ph..... phenyl (C_6H_5-)

ppm..... *Spec.* parts per million.

i-pr..... *iso*-propyl.

q..... *Spec.* quartet.

rt..... room temperature.

s..... *Spec.* singlet.

Spec..... spectroscopy.

t..... *Spec.* triplet.

TBAF..... tetra-*n*-butylammonium fluoride.

THF..... tetrahydrofuran.

THP..... tetrahydropyranyl.

TLC..... thin layer chromatography.

TMS..... *Spec.* tetramethylsilane.

TPAP..... tetra-*n*-propylammonium perruthenate.

UV..... ultra violet.

Abstract.

It has been demonstrated that phosphinamides such as (**29**) are efficient catalysts for the asymmetric reduction of prochiral ketones with borane. Reduction typically occurs in less than 1 hour at room temperature with modest asymmetric induction.

An investigation into the steric and electronic factors important for catalysis has revealed that the greatest reduction accelerations are achieved by derivatives in which the 'R^2-N-P=O' structural unit can adopt a planar geometry, thus maximising electron donation from the nitrogen lone pair to the P=O bond. Electron withdrawing substituents on the nitrogen atom of the N-P=O unit decreases both the rate of catalysis and reduction selectivity. An electron rich substituent bonded to phosphorus dramatically increases the rate of catalysis with little effect on selectivity. Conversely, an electron withdrawing substituent bonded to phosphorus has a detrimental effect on both rate of catalysis and enantiomeric induction.

On the basis of experimental and theoretical data it is proposed that catalysis is achieved by activation of borane *via* a strong donation from the oxygen atom of the N-P=O system coupled with a much weaker interaction of the carbonyl group lone pair electrons with the phosphorus atom.

We have also demonstrated that a combination of the phosphinamides with an electron accepting boronate ester, either as a bi-molecular co-operative system ((**98**) together with (**29**)) or as a single molecular entity (**108**), significantly improves asymmetric induction, presumably as a consequence of more effective ketone binding.

Finally, we have shown that Diphenylphosphinyl group is an effective protecting group for primary α-amino ketones and that the ketophosphinamide products are excellent substrates for diastereoselective reduction with borane. The diphenylphosphinyl group both activates the borane reagent for hydride transfer and directs the intramolecular reduction.

1 Introduction.

Asymmetric Synthesis: why it is important and how it can be achieved.

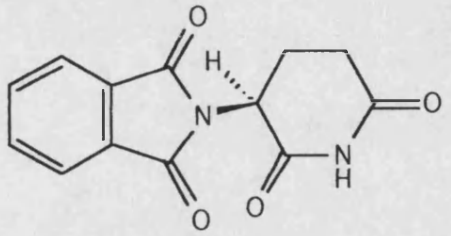
Section 1.1 The Phenomenon of Chirality.

Chirality is a fundamental symmetry property of three dimensional objects. In a chemical context, chirality refers to the three-dimensional structure of a molecule. Many molecules can occur in two different enantiomeric forms, differing in the spatial arrangement of the carbon atoms or groups, such that they are related as object to mirror image. In the absence of an external chiral influence both enantiomers have identical chemical properties and differ only in the direction in which they rotate the plane of plane-polarised light.

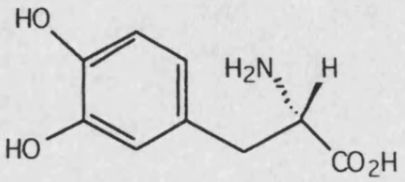
The demand for a flexible and easy route to homochiral compounds comes from the relationship between the absolute configuration of organic molecules and their biological properties. In much the same way that a right-handed glove will only fit the right hand, enzymes, cell receptors and all other molecular components of life are themselves constructed from molecules of a single "handedness" and are therefore sensitive to differences of configuration between molecules with which they interact. Many biologically active compounds, such as drugs, contain one or more stereogenic centres. When a chiral drug interacts with its receptor site, which is also chiral, the two enantiomeric forms of the drug interact differently and may lead to different effects. Thalidomide (**1**) is perhaps the most dramatic example of a drug whose two enantiomers have profoundly different effects; the R-antipode provided the desired clinical response as an anti-emetic whereas the S-enantiomer was found to be responsible for the horrifying series of birth defects that occurred among children born in the late 1960's.[1]

DOPA (**2**) is used in the treatment of Parkinson's disease. The active drug is

the achiral compound dopamine, formed by the enzyme-mediated decarboxylation of (**2**), but this cannot cross the blood-brain barrier to reach the required site of action. The "prodrug" (**2**) can and is then decarboxylated by the enzyme dopamine decarboxylase. The enzyme is, however, specific for the (-) enantiomer of (**2**). It is therefore essential to administer only DOPA as the pure (-) stereoisomer to prevent a harmful build up of (+)-(**2**) which cannot be metabolised by the enzyme.[2]

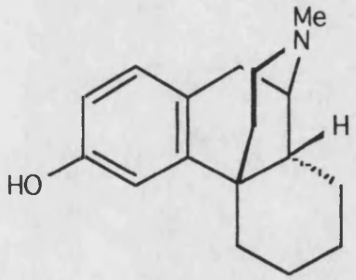


(1)

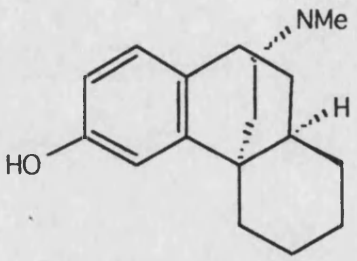


(-)-DOPA (2)

For many compounds two enantiomers can have quite different and distinct biological activities, for example the alkaloid (-) levorphanol (**3**) is a powerful narcotic analgesic. Its enantiomer (+) dextrorphan (**4**) has no analgesic activity, but is active as a cough suppressant.



(3)



(4)

There is increasing awareness in the pharmaceutical and medicinal chemical industries that neglect of stereochemistry results in a collection of worthless data. This leads to misleading conclusions and the waste of research time in the generation of "sophisticated nonsense" and hence inferior products.[3b] It is now appreciated that the pharmacologically less active or inactive isomers may well contribute to the toxicity or adverse effects of the drug. As a result legislation

demands that on registration of a new compound the chirality of the drug substance is recognised, and the stereoisomer responsible for the activity of interest identified. Stereochemical considerations must be added to the specification of the drug substance, including assignment of absolute configuration, and detailed information on how the chiral centre is created. The most important addition to the normal requirements for drug approval is the need to "justify on chemical, pre clinical and clinical grounds the stereoisomeric form(s) chosen for marketing".[3]

It is therefore of prime importance to be able to control the formation of asymmetric centres during the course of a synthesis. Especially delicate is the formation of the first stereocentre in a chiral molecule, and the past 15 years have seen an explosion of methods for achieving this goal.[4]

Section 1.2 The Preparation of Chiral Compounds.

There are various procedures used to prepare homochiral compounds:

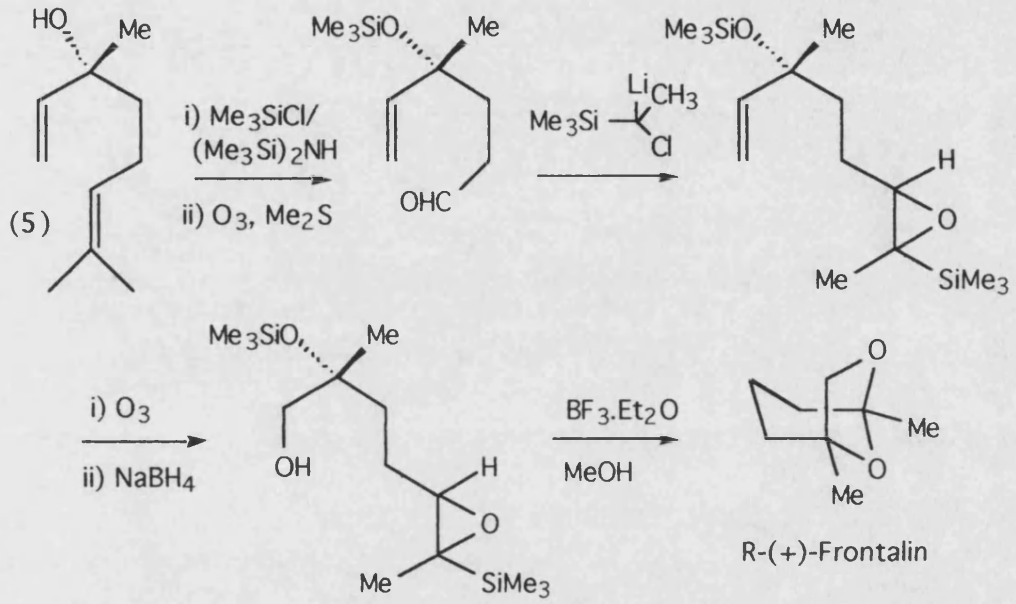
1.2.1 Resolution of Racemic Mixtures.

Resolution may be thought of as the classical method of obtaining homochiral compounds. The procedure involves the derivatisation of the mixture with an enantiomerically pure resolving agent, then separation of the resulting diastereomeric compounds. The major disadvantage of this method is the "trial and error" element of finding a suitable resolving agent, and the fact that the required stereoisomer cannot be obtained in greater than 50% yield. This results in a serious waste of material on a large scale.

1.2.2 Modification of Naturally Occurring Compounds.

The ultimate source of chirality in all asymmetric synthesis is nature. The

chiral compounds that occur in nature provide an enormous range and diversity of possible starting materials. Modification of naturally occurring molecules from nature's "chiral pool" such as amino acids, sugars, alkaloids and terpenes has been used very effectively in asymmetric synthesis.[4] An example is the synthesis of R-(+)-frontalin from naturally occurring R-(-)-linalool (**5**) by Magnus and Roy (Scheme 1).[5]



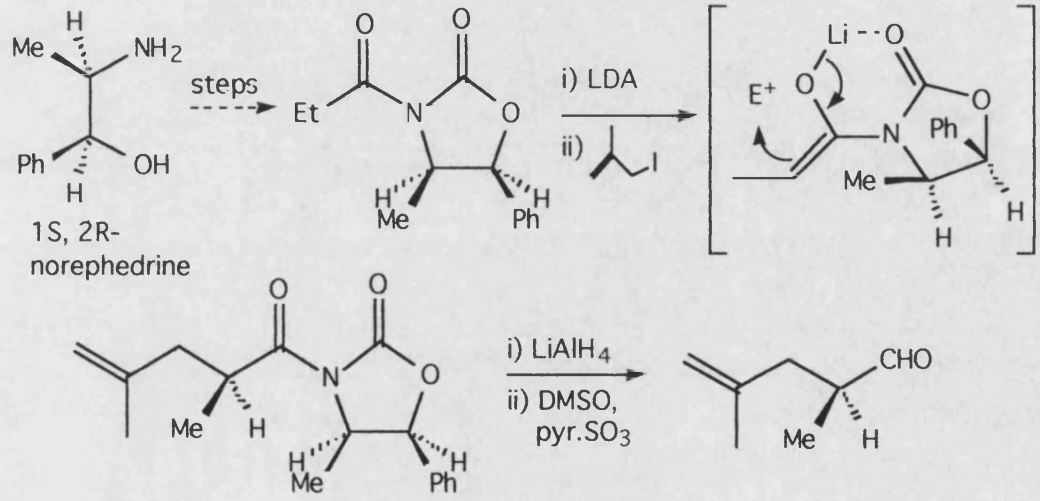
Scheme (1)

1.2.3 Asymmetric Synthesis.

Two distinct methods are used to achieve this. The first is the use of a chiral auxiliary. The enantiomerically pure auxiliary is attached to an achiral substrate and used to direct the reaction and hence induce chirality into the molecule. It is then removed and can be recovered and recycled. Ideally both enantiomers of the chiral auxiliary must be available in enantiomerically pure form, and must be easily added and removed without racemisation of the induced chiral centre or the auxiliary itself. An example is the oxazolidinone methodology developed by Evans,[6] which has been used successfully for many asymmetric transformations including aldol

reactions,[6a] Diels-Alder reactions [6b] and alkylations.[6c]

The power of this methodology was demonstrated by Evans in his elegant synthesis of the Prelog-Djerassi lactone,[7] the first stage of which involves the alkylation of the oxazolidinone derived from norephedrine (Scheme 2). Reaction of the internally chelated Z-enolate of the oxazolidinone with methallyl iodide occurs on the face opposite the methyl and phenyl groups of the auxiliary. The resultant 97:3 mixture of diastereoisomers could then be purified to a ratio of >500:1. This illustrates a significant advantage of the auxiliary methodology in that the reaction products are diastereomeric, and hence can be separated and purified.



Scheme (2)

The second method is asymmetric catalysis,[8] which unlike stoichiometric methods, is capable of multiplying chirality. In this process, the reaction proceeds *via* a non-covalently bound complex between catalyst and substrate.

Section 1.3 The Principle of Asymmetric Catalysis.

Consider a prochiral molecule (A) with enantiotopic faces (Figure 1) which on addition of reagent (B) is transformed into a product (P); the reaction being catalysed by an organometallic complex (M).

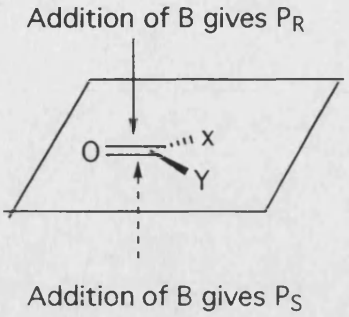
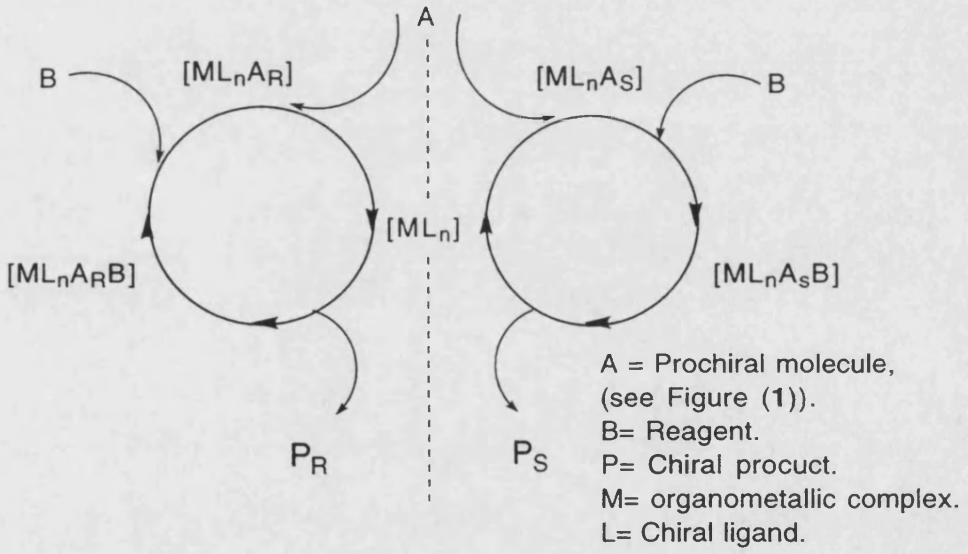


Figure (1)

If the catalyst is achiral, P will be obtained as a racemic mixture $P_R + P_S$; one catalytic cycle will result in formation of one enantiomer of the product, the other enantiomer being obtained with the same probability in a catalytic cycle independent or connected to the first (Figure 2).



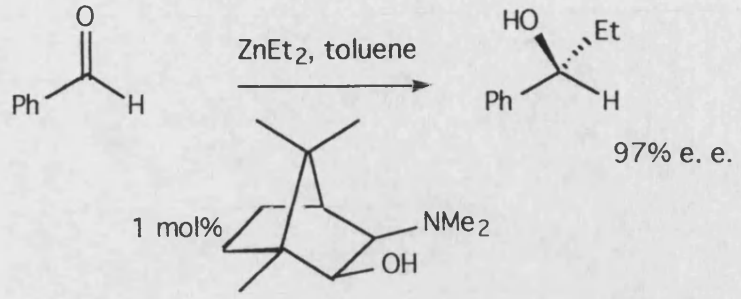
Reaction A+B ⟶ P, catalysed by $[ML_n]$

If ligand, L, is racemic $[P_R]=[P_S]$
If ligand, L, is non racemic $[P_R]\neq[P_S]$

Figure (2)

The two cycles are mirror images of each other. If the catalyst is modified by introduction of a chiral ligand, the two competitive cycles remain, but are no longer mirror images of each other, and their relative efficiencies must differ. A good choice of ligand should increase the rate of formation of one enantiomer of product over the other resulting in increased enantioselectivity. An example is the

addition of diethyl zinc to aldehydes catalysed by chiral amino alcohols (Scheme 3).[9]



Scheme (3)

Of the methods currently available for asymmetric synthesis, catalytic processes are the subject of intensive research at the present time. By definition the catalyst can be recovered unchanged at the end of the reaction and in many cases only a small quantity is required to direct a reaction, although in practice a larger quantity may be used to achieve a reasonable rate of conversion. The possibility of using sub-stoichiometric quantities of an enantiomerically pure compound to direct an asymmetric transformation obviously has great attractions for large scale industrial use where cost and environmental issues are critical. This thesis involves the study of an catalytic asymmetric transformation, namely the asymmetric reduction of prochiral ketones. The area of enantioselective carbonyl reduction has been studied extensively over the past 10 years though the majority of work has been centred on the use of stoichiometric methods. A detailed summary of the major advances in this area of asymmetric synthesis is given below.

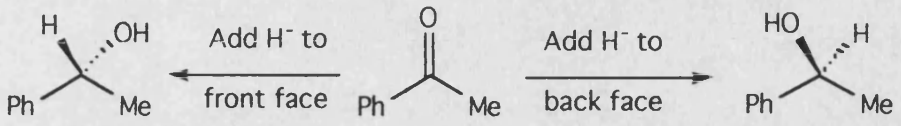
The Asymmetric Reduction of ketones.

Section 1.4: Asymmetric Carbonyl Reduction and How it can be Achieved.

The reduction of unsymmetrical ketones to homochiral alcohols is one of the

most widely studied and synthetically important reactions in asymmetric organic synthesis.[10] The alcohols produced by such a process may be used as a chiral framework for a synthesis, or may be valuable products in their own right.

For ketone reduction, addition of hydride to one face of the carbonyl group gives an alcohol of one absolute configuration; addition to the opposite face gives the other enantiomer (Figure 3).



(R) (S)

Figure (3)

A variety of reagents has been developed over the last decade which control the selective addition of hydride to one of the two enantiotopic faces of the carbonyl group; many have been developed by chiral modification of common reducing agents such as lithium aluminium hydride, sodium borohydride, and borane.[10b]

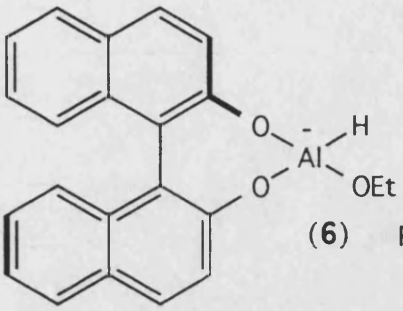
Section 1.4.1 Stoichiometric Reagents.

The most obvious method of controlling face selectivity for hydride delivery is the use of an enantiomerically pure hydride source. In principle these reagents will transfer hydride to each face of the ketone through two diastereomerically distinct transition states, one of which should be lower in energy than the other. Two examples of a successful application of this expedient are chiral aluminium hydride reagents[10c,e] and organoboranes.[10g]

1.4.1.1 Aluminium Hydride Reagents.

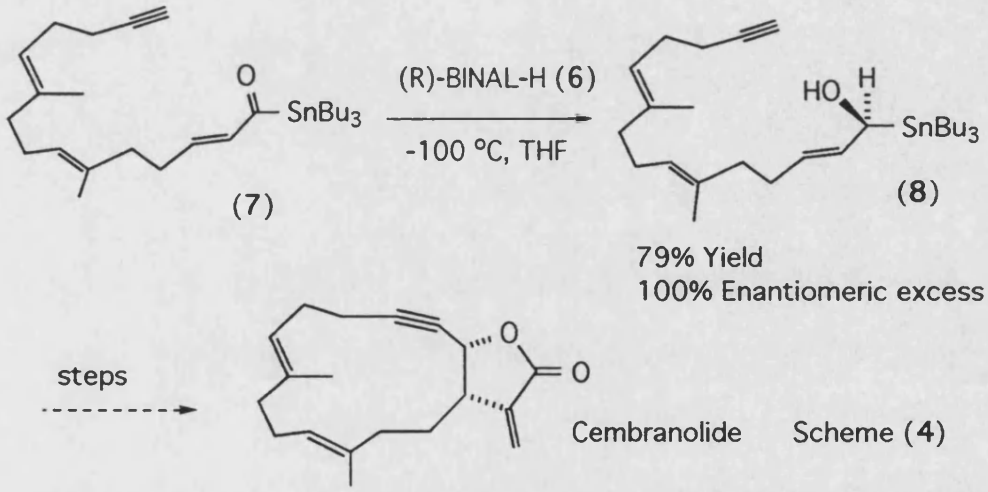
BINAL-H (**6**) was developed by Noyori [11] and is a modification of lithium aluminium hydride in which two hydrides are replaced by the chiral diol R-[1,1'-

binapthyl]-2,2'diol and a third by a simple alcohol.



(6) R- BINAL-H

The reducing agent exhibits extremely high face selectivity in the reduction of variety of aromatic, alkynylic and olefinic ketones. For example the reduction of tributylstannyl ketone (**7**) gives a single enantiomer of alcohol (**8**) which has been used in a concise synthesis of the cembranolides, a class of marine diterpenoid natural products (Scheme 4).



(7) (8)

79% Yield
100% Enantiomeric excess

Cembranolide Scheme (**4**)

The high selectivity is achieved through the intermediacy of a transition state in which a stabilising interaction occurs between the trialkyltin and ethoxy- groups, directing hydride from aluminium to one face of the ketone (Figure 4).[12]

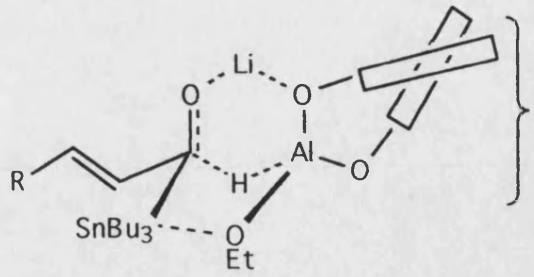
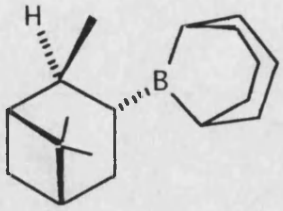


Figure (4) Transition state for ketone reductions by (6)

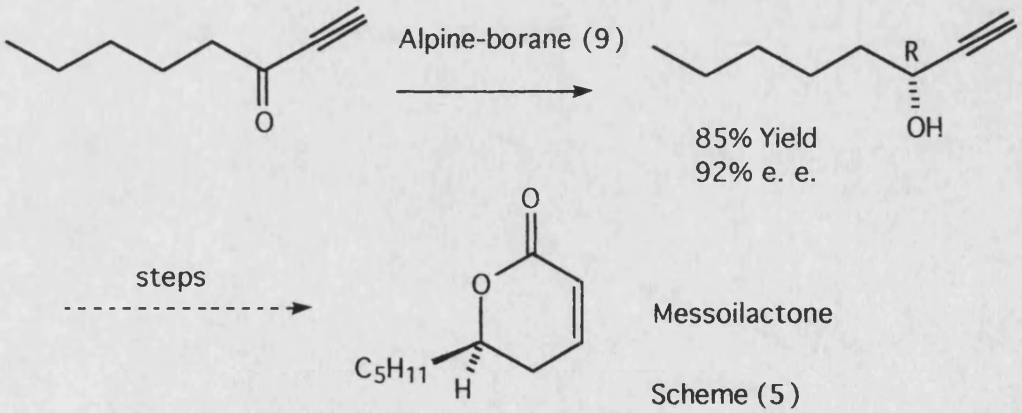


Alpine-borane (9)

1.4.1.2 Organoboranes.

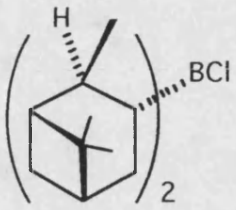
The other outstanding source of "chiral hydrides" are enantiomerically pure alkylboranes.[10g,13] These are readily available from hydrocarbon precursors, and numerous structural variations have been reported. Of these the β-3-pinanyl-9-borabicyclo[3.3.1]nonane reagent (**9**) (commonly known as Alpine borane) developed by Midland is one of the most successful in terms of substrate scope and selectivity.

Like many trialkylboranes, Alpine borane is virtually inert to various functional groups, but is very effective for controlling asymmetric reductions particularly of acetylenic ketones.[13] The acetylene group can then be subsequently transformed to give a vast range of target molecules; in the example shown messoilactone, the defence allomone of the formicine ant, is the synthetic target (Scheme 5).



Scheme (5)

One of the drawbacks of the Alpine borane reagent is that it is not very reactive towards ketones. Its reactivity can be increased by increasing the Lewis acidity of the boron atom. Brown has utilised this effect in developing a variety of dialkylhaloboranes; chlorodiisopinocampherylborane (**10**) (IPC_2BCl) being by far the most efficient.[14]



Chlorodiisopino campherylborane (10)

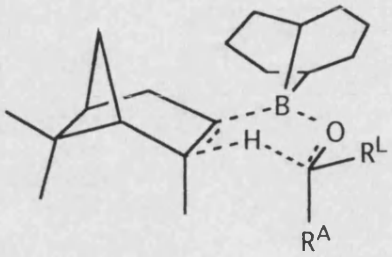


Figure (5) Transition state for ketone reductions by (9)
R^L=large group, R^A=alkyne

Both reagents (**9**) and (**10**) are thought to work in a similar fashion and distinguish the two faces of a prochiral ketone on the basis of substituent size. In the case of (**9**) a six-membered boat-like transition state, in which the hydride β- to the boron atom is transferred to the ketone, has been proposed. The larger of the ketone substituents (R_L) occupies a pseudo-equatorial position so as to minimise 1,3-diaxial interactions (Figure 5). This results in a very high face selectivity.

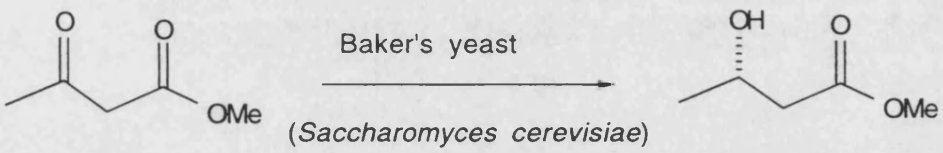
Section 1.4.2 Catalytic Reagents.

All the above examples, despite their high efficiency and the high levels of asymmetric induction they impart, suffer one major drawback; namely they are all stoichiometric reagents. In other words one molar equivalent of chiral reducing agent is required for the transformation. On a large scale this may be prohibitively expensive and complications arising from the large quantities of reagent required may render them unusable. Far more attractive is a catalytic system in which a sub-stoichiometric quantity of chiral directing ligand can be used in conjunction with a

reducing agent. The catalyst can then, in theory, be recovered and recycled. Various reducing systems have been developed to this end.

1.4.2.1 Enzyme Mediated Reduction.

In recent years there has been a veritable renaissance in the field of enzymology due in part to the realisation that many enzymes will accept 'unnatural substrates'. The asymmetric reduction of ketones, usually conducted with whole cells (normally yeasts) have proved very successful.[15] Baker's yeast (*Saccharomyces cerevisiae*) has been used for the reduction of simple aryl ketones and α-haloketones, but most effectively for β-keto esters and β-keto acids (Scheme 6).[15c]



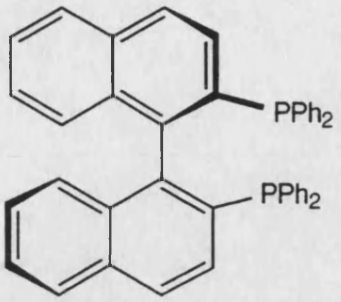
100% Yield
97% e. e.

Scheme (**6**)

Enzymatic reduction is, however, limited with respect to substrate suitability. Also it is not always possible to access both enantiomers of product using enzymatic procedures.

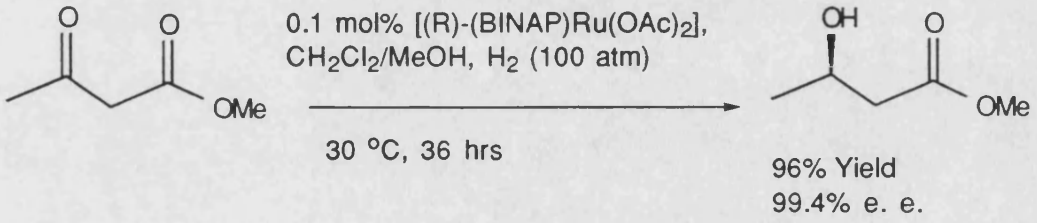
1.4.2.2 Synthetic Reduction Catalysts.

In developing a synthetic reduction catalyst the aim is to mimic the action of an enzyme both in terms of selectivity and functional group specificity and to combine with this an ability to accept a wide range of ketone substrates. Synthetic chemists have developed a number of catalytic systems which satisfy these criteria.



R-BINAP (**11**)

One such reagent is the chiral phosphine BINAP[16a] (**11**) developed by Noyori. BINAP is chiral by virtue of a biaryl linkage about which rotation is restricted, and is available in both enantiomeric forms. Complexes of BINAP and ruthenium have been used to direct the asymmetric hydrogenation of alkenes and ketones with extremely high selectivity (Scheme 7).[16d]



Scheme (**7**)

The major limitation with this methodology is that the substrate must contain a suitable co-ordinating group, such as an ester, in close proximity to the keto group in order to achieve good enantioselectivity.[16d] Hydrogen is then transferred from metal to substrate in a well defined asymmetric environment centred on ruthenium (Figure 6). An example of an application of this methodology is the asymmetric synthesis of carnitine[16c] (vitamin B_T), a compound responsible for human metabolism of long chain fatty acids (Scheme 8).

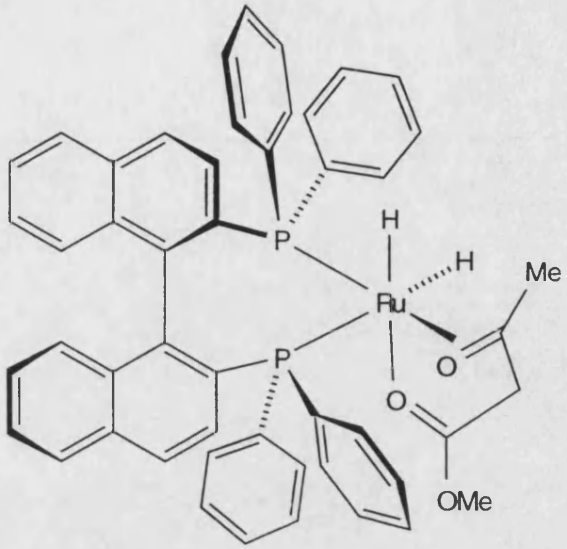
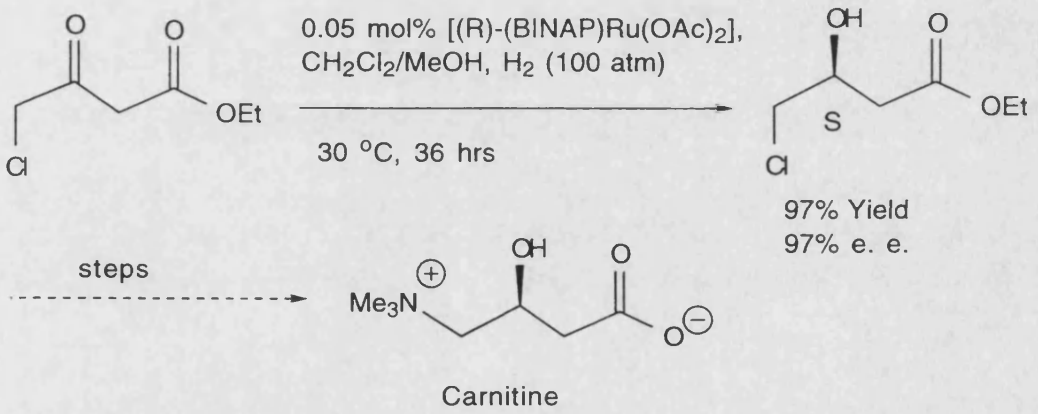


Figure (**6**) Substrate bound to ruthenium/ BINAP catalyst prior to asymmetric reduction.

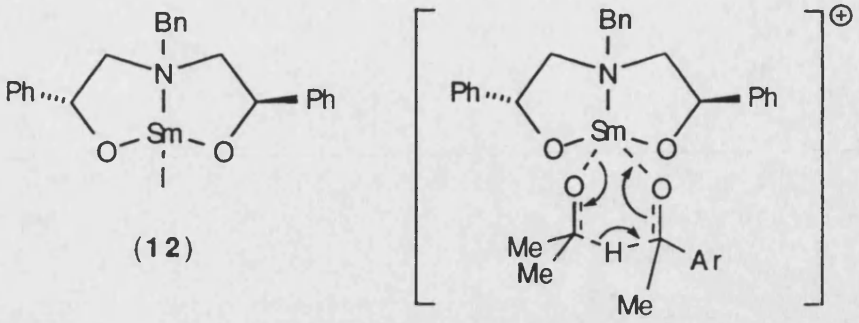


Carnitine

Scheme (**8**)

Another recent development in the field of metal based catalysts uses an alcohol as the primary reducing agent in a Meerwein-Ponndorf-Verley type reduction.[17] The samarium based variation of this reaction has been developed by Evans using the complex (**12**) formed from the appropriate chiral amino diol and samarium triiodide.

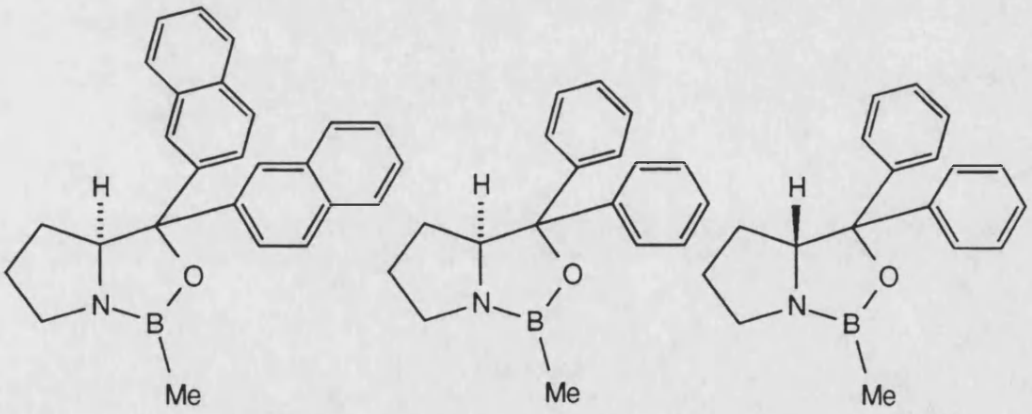
This promotes the reduction of aryl/alkyl ketones using isopropyl alcohol as reductant with enantiomeric excesses up to 97%, presumably via a transition state similar to that shown (Figure 7).[18]



(12)

Figure (7) Transition state for reduction of aryl/methyl ketone by isopropylalcohol catalysed by (12)

By far the most widely used and powerful reduction catalyst is based on the oxazaborolidine structure first reported by Itsuno[19], and later by Corey who identified the structure and mechanism by which reduction takes place.[20] The oxazaborolidines (**13**)-(**15**) contain adjacent donor (nitrogen) and acceptor (boron) sites, and are not in themselves reducing agents; they require borane as the stoichiometric reducing agent. The catalysts mimic an enzyme in that they bind ketone (in the acceptor site) and borane (in the donor site), bringing them together, allowing them to react in an asymmetric environment and releasing them.

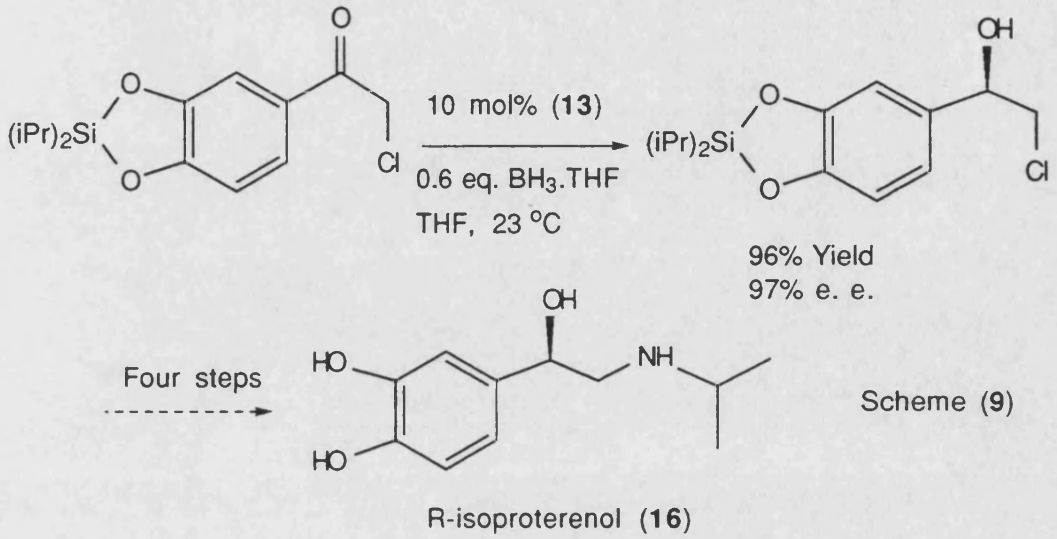


(13) (14) (15)

The proline derived reagents shown were developed by Corey[20], and catalyse the reduction of a wide range of ketones with enantiomeric excesses of

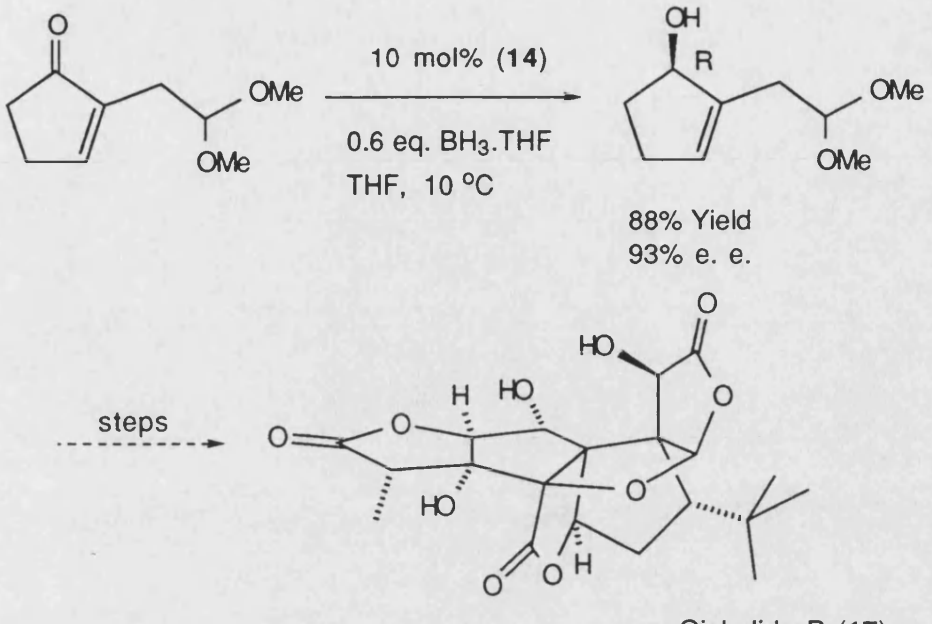
>95%.[20b] Numerous modifications of the basic oxazaborolidine structure have been reported over the past few years, all with varying degrees of efficiency.[21]

The oxazaborolidine catalysed reduction has been used as the key step in countless asymmetric syntheses, an early example being the synthesis of the β-adrenoreceptor agonist Isoproterenol (**16**) (Scheme 9).[22]



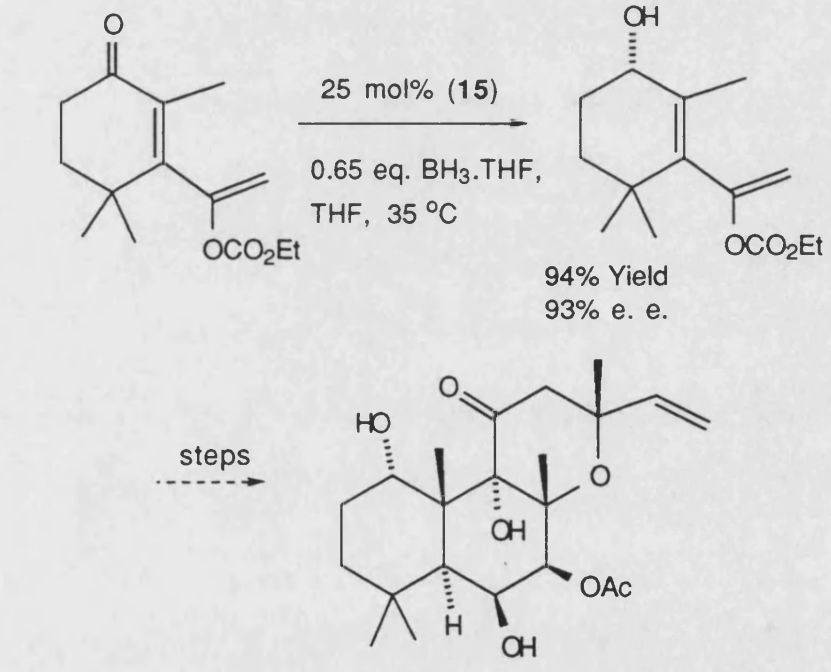
Scheme (**9**)

More recently the synthesis of highly complex molecules have been realised using oxazaborolidine catalysed reduction as a key step. The new chiral centre thus created subsequently determines the absolute stereochemistry of the final product. Two such examples are the synthesis of Ginkolide B (**17**),[23] a potent agonist of platelet activating factor, and Forskolin (**18**),[24] an activator of ATP-AMP cyclase and therefore capable of controlling cellular levels of cyclic AMP (Schemes 10a and 10b).



Ginkolide B (**17**)

Scheme (**10a**)



Scheme (**10b**) Forskolin (**18**)

In all the above examples, ketone substituent size is important in determining the reduction selectivity. The ketone is assumed to co-ordinate with the electron poor boron atom through its lone pair *trans* to the large carbonyl appendage (phenyl in the case of acetophenone), with the borane co-ordinated to the adjacent

donor nitrogen atom (Figure 8).[25] Both ketone and borane co-ordinate to the convex face of the catalyst which serves both to activate the reagents, and bring them within reactive distance of each other. Of the two possible transition states shown in Figure 8, the latter is disfavoured due to a strong steric interaction between the substrate methyl group and the catalyst phenyl ring, while the other is much less hindered.

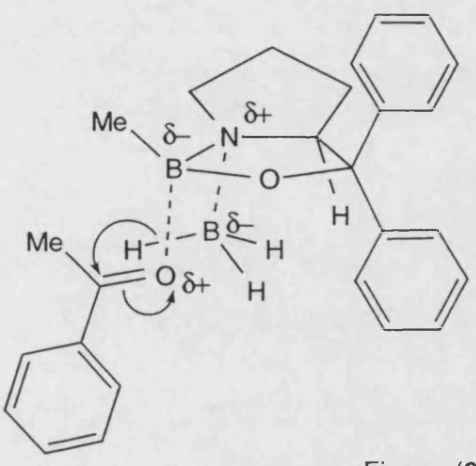
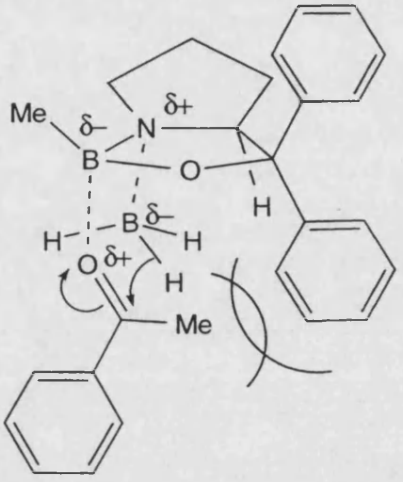


Figure (**8**)

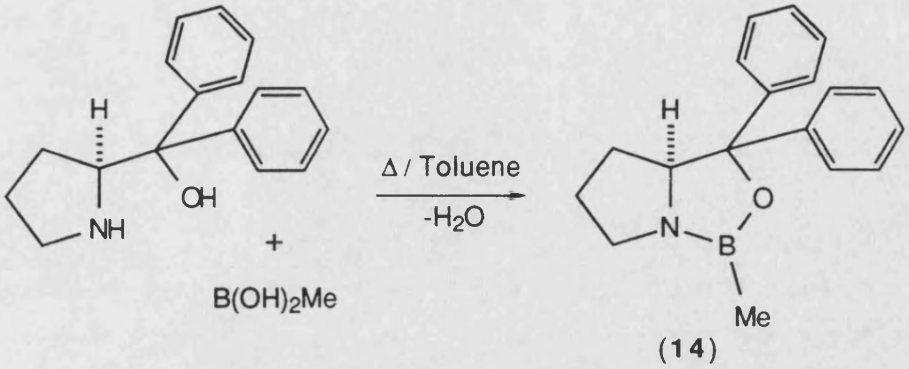


Disfavoured transition state for reduction by (**14**).

Hydride is thus directed onto one face of the ketone selectively *via* a six membered transition state. Once reduction has taken place, the catalyst releases product and is then free to re-enter a catalytic cycle, reducing more ketone. The reducing system is a good example of the 'ligand acceleration phenomenon'[26] i.e. neither borane (stoichiometric reductant) nor the oxazaborolidine (catalyst) reduces ketone rapidly but a combination of these reagents form a complex which, in the case of acetophenone, results in quantitative reduction in a few minutes at room temperature.

Despite the effectiveness and apparent ubiquitous nature of the oxazaborolidine system there are a few disadvantages, mainly concerned with preparation. The traditional synthesis involved reaction of the appropriate amino

alcohol with a boronic acid in boiling toluene, with azeotropic removal of water (Scheme 11).[20g]

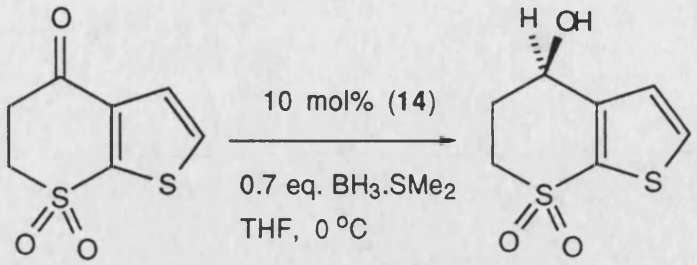


(14)

Scheme (11)

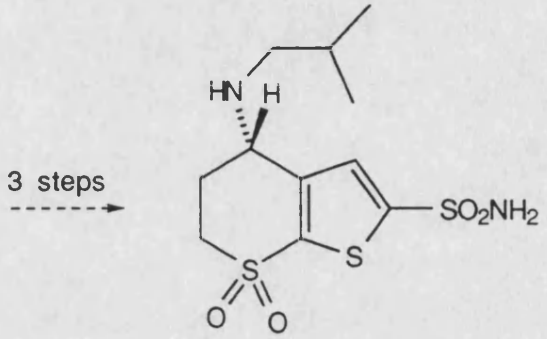
This preparation has proved problematic for many groups; the catalyst prepared *via* this route affording erratic and non reproducible results, largely due to traces of unreacted boronic acid, and various alkoxy borane impurities.[27,29] In a detailed study of the performance of oxazaborolidine (**14**), a group of Merck chemists found that traces of methylboronic acid or unreacted amino alcohol had a detrimental effect on catalyst efficiency, with a substantial erosion of enantioselectivity.[28] They also found that <<1 mol% of water was deleterious to enantioselection. In the reduction of (**19**), an intermediate in the synthesis of the carbonic anhydrase inhibitor MK-0417, it was found that under the conditions shown as little as 1 milligram of water per gram of ketone was sufficient to lower the enantiomeric excess from 95% to 50% (Scheme 12).[28]

The oxazaborolidine catalysts thus require rigorous exclusion of water during use and careful preparation and purification. This presents a serious limitation for large scale and industrial application.



(19)

98% Yield
96% e. e.



MK-0417 Scheme (12)

Development of an Alternative Catalyst for the Asymmetric Reduction of Ketones with Borane.

Section 1.5 Rationale and Catalyst Design.

Obviously no one reagent can be expected to provide all the desired traits one would like in a reducing agent. As synthetic targets become more complex so the demand for new systems, complementary to those currently available, which can offer both high levels of selectivity and specificity and tolerate the presence of other sensitive functionality in complex substrates increases.

Our work in this area was promoted by the need for a catalytic reducing system based on borane as the stoichiometric reductant, which would be less susceptible to reaction conditions and easier to prepare and purify than the oxazaborolidines. With these goals in mind we envisaged replacing the -BR- component of these systems with a P(O)R unit, as typified by the phosphinamide structure shown (Figure 9).

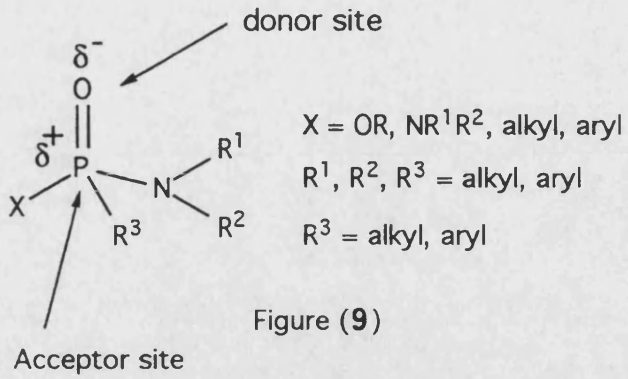
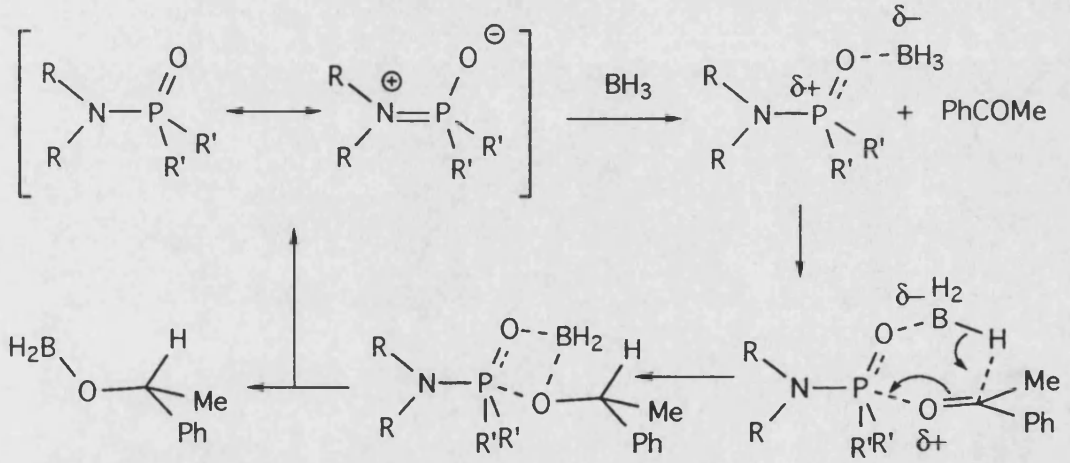


Figure (**9**)

This structural fragment still has the essential requirements of the oxazaborolidine system, i. e. a suitable donor site in the oxygen atom of the P=O bond, and an adjacent acceptor site on phosphorus. These similarities, we believed, would result in a similar mechanism of action and reactivity profile (Scheme 13).



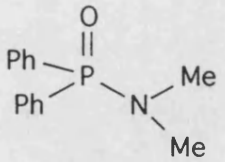
R=R'= alkyl, aryl

Scheme (**13**)

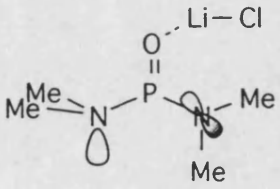
There is a significant donation of electron density from the nitrogen lone pair to the P=O bond in phosphinamides, though unlike the corresponding carboxylic amide nitrogen atom, phosphinic amide nitrogen is more basic since the lone pair is less involved in π-bonding to phosphorus.[30] The geometry and protonation behaviour of carboxylic amides is interpreted in terms of resonance effects, resulting in the partial double bond character of the nitrogen acyl linkage. In amides derived from phosphoric acid $R_2P(O)NR_2$, conjugation effects are

expected to be less important because of the different atomic orbitals (2*p* and 3*d*) involved. The lesser involvement of the nitrogen lone pair in conjugation with the phosphinyl group is taken as a key factor responsible for the remarkably facile cleavage of the P-N bond under acidic conditions.[31] Such π-bonding is not entirely absent however since in some instances $R_2P(O)NR_2$ compounds show restricted rotation about the P-N bond, for example phosphinamide (**20**); the crystal and molecular structure of which has been determined.[32] The large π–interaction of the nitrogen lone pair electrons with the phosphorus *d*-orbitals in this compound results in a shortening of the P-N bond length to 1.168Å and an elongation of the P=O bond distance to 1.482Å, which is longer than normal phosphoryl bonds.[33,56]

Though the nitrogen atom is fairly basic in these compounds, a number of X-ray crystal structures of related phosphinamide structures complexed to lithium[34] and lanthanide[35] cations have been reported e.g. (**21**) and (**22**). In these systems complexation is invariably through the oxygen atom, with no evidence of nitrogen co-ordination. It therefore seemed likely that the oxygen atom in the N-P=O system would be an effective donor for electrophilic reagents such as borane (Scheme 13).

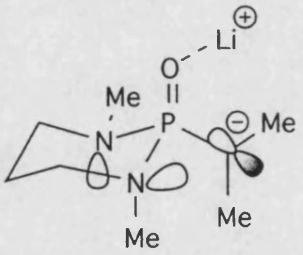


(20)

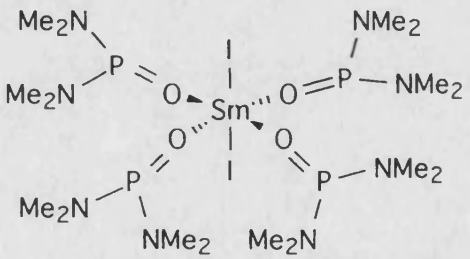


Third NMe_2 omitted

$[ClLi.O=P(NMe_2)_3]_4$



(21)



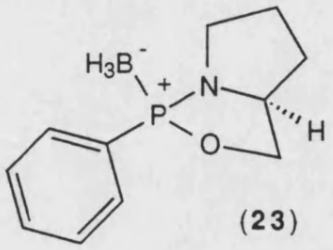
$[SmI_2(HMPA)_4]$

(22)

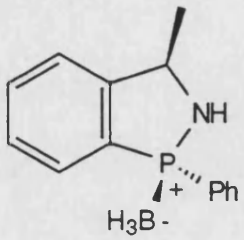
Third NMe_2 omitted

Co-ordination of the oxygen atom to a molecule of borane should increase the level of positive charge at the phosphorus centre, making it more electrophilic and a better acceptor of electron density from the carbonyl group lone pair (the phosphorus atom in these systems is not usually regarded as a Lewis acid of any appreciable strength).[76] Assuming the sequence of events in Scheme 13 above, the borane and ketone will be located within reactive distance of one another, and hydride transfer can then occur through a six membered transition state. Manipulation of groups attached to nitrogen and phosphorus should enable a suitable chiral environment tc be generated, allowing selective delivery of hydride, in an absolute sense, to one face of the ketone.

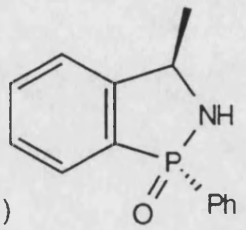
The phosphinamide structures reported in the literature are all stable to air and moisture and are usually crystalline solids.[36] No phosphinamide-borane complexes have been reported,[116] though a single report of a borane protected oxazaphospholidene (**23**) being used as an asymmetric reduction catalyst was described by Buono,[37] however, no explanation of the mechanism of reaction was discussed.



(**23**)



(**24**)



(**25**)

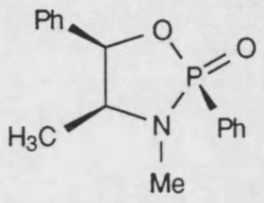
Prior work In the Wills group had demonstrated that the dihydobenzazaphosphole-borane complex (**24**), prepared via *ortho*-lithiation of the silyl-protected amine,[53] had a controlling influence on the reduction of acetophenone; the presence of 2 mol% of this compound in conjunction with borane dimethylsulfide complex in THF at room temperature gave a 2:1 mixture (ca. 30% e. e, R- major) of enantiomeric alcohols. In a very preliminary result it was also found that the corresponding phosphine oxide (**25**) had some catalytic activity.[55]

Since compounds structurally related to (**25**) are easier to prepare and handle than the P(III) complexes, we planned to execute a detailed study of the factors important for both catalysis and asymmetric induction in the corresponding P(V) system by structural modification of a series of simple analogues of the basic phosphinamide subunit. For example variation of the steric bulk of both the nitrogen and phosphorus substituents and the electronic properties of the R_2N-P=O structural unit. Analysis of conformational effects by preparation of simple cyclic systems should also, we felt, give an insight into the mechanism of catalysis and aid the design of a more rigid chiral environment around the phosphorus centre.

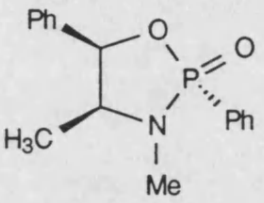
2 Results and Discussion.

Section 2.1: Initial Study.

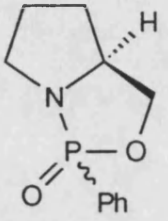
Oxazaphospholidines (**26**) and (**27**) satisfied the structural requirements of our proposed catalyst. These compounds were prepared as a 1.25:1 mixture of diastereoisomers, *via* a literature procedure, from 1R, 2S-ephedrine and phenylphosphonic dichloride and were separated by column chromatography.[38,62a] However both compounds were found to be unstable to the reaction conditions employed (0.6 equivalents of BMS, THF, rt), presumably as a consequence of reduction by borane.



(**26**)

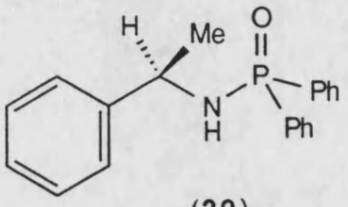


(**27**)



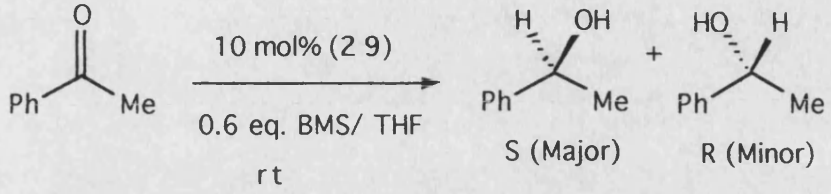
(**28**)

Similar results were obtained with the prolinol derived oxazaphospholidine (**28**) prepared from S-prolinol and phenylphosphonic dichloride;[39] an equimolar mixture of diastereoisomers decomposed within 20 minutes at room temperature on addition of BMS (as assesed by TLC). We suspected that the oxygen-phosphorus bond in these compounds may be reactive to borane[120] and turned our attention toward the acyclic phosphinamide (**29**).



(**29**)

This compound was prepared in 89% yield as a crystalline solid by the reaction of (R)-(+)-α methylbenzylamine with diphenylphosphinic chloride (triethylamine, DCM, rt,), and appeared to be stable to reaction conditions. Sub-stoichiometric quantities of this compound were found to catalyse the reduction of acetophenone by BMS (Scheme 14).[54]



82%, 26% e. e.

Scheme (1 4)

Addition of 10 mol% of (**29**) together with 0.6 equivalents of BMS resulted in >98% reduction of acetophenone in less than 60 minutes at room temperature. The progress of the reaction was followed using HPLC with a UV detection system (Figure 12). Since the molar extinction coefficient of the ketone is some 50 times that of the alcohol, a 1:1 ratio of ketone to alcohol represents a conversion of >98%. This acts as a convenient marker for the qualitative comparison of catalyst performance and was used to compare the examples described throughout, although in all cases where the time was less than 1 hour, *no acetophenone* could be detected in the reaction mixture after this time. In contrast uncatalysed reduction required some 14 hours under the same conditions to proceed to the same extent. The resulting alcohol consisted of a 1.7:1 mixture of enantiomers (26% e.e., S- major, 82% yield) as assessed by both comparison of the optical rotation with reported literature values and chiral HLPC.[40]

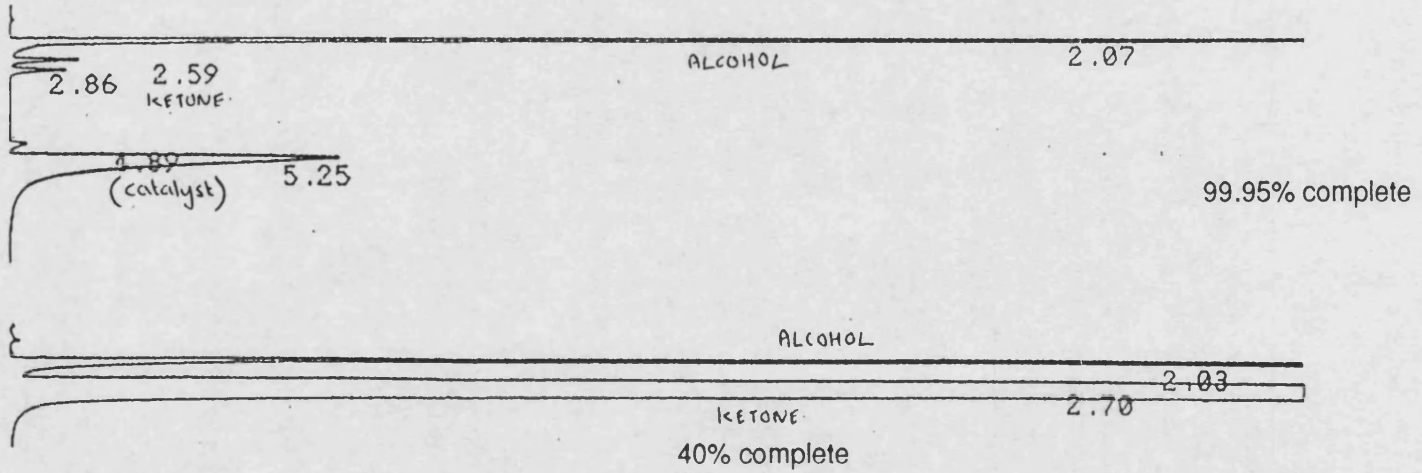
Encouraged by the dramatic acceleration of the reaction obtained on adding the phosphinamide, the utility of (**29**) was then further investigated by varying catalyst concentration and reaction conditions (Table 1).

Figure **12** HPLC Separation of Acetophenone and 1-Phenylethanol.

Conditions:

Column:	Techspere 5 ODS C18
Mobile Phase:	37% Acetonitrile/water
Flow Rate:	2 cm^3min^{-1}
Injection:	5 µl
Detection:	UV at λ=254 nm
Temperature:	Ambient

HPLC analysis after 1 hour: (Ketone 50X UV absorption of alcohol at 254 nm)



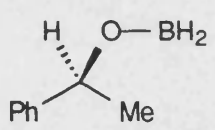
Mol% catalyst (29)*	Temp.	Solvent	Time (>98% reduction)	Yield (isolated)	e.e, (config.)
0	rt	THF	> 12 hrs	75%	-
10	rt	THF	< 1 hr	82%	26% (S)
2	rt	THF	1.5 hrs	75%	23% (S)
100	rt	THF	<30 min	69%	13% (S)
2	rt	Toluene	2 hrs	88%	30% (S)
2	rt	DCM	2.5 hrs	77%	18% (S)
10	0 °C**	THF	3 hrs	75%	20% (S)
10	60 °C	THF	< 1 hr	79%	18% (S)

* 0.6 equivalents of BMS added to a 1M solution of ketone and catalyst.
** Catalyst partially precipitated at this temperature.

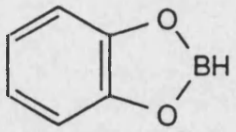
Table 1 Reduction of Acetophenone catalysed by (**29**).

Variation of reaction solvent appeared to have little effect on reduction rate and a marginal effect on selectivity, with DCM being the least favourable. Increasing the temperature appeared to have a detrimental effect on selectivity, whilst at 0°C partial precipitation of catalyst occurred resulting in both reduced rate of catalysis and enantioselectivity. In all cases the enantiomeric excesses were modest, but the relatively small difference in selectivity obtained when the catalyst concentration was reduced to 2 mol% suggested that virtually all the reduction was proceeding through the catalyst mediated pathway even at the lower concentration.

Since alkoxy-borane complexes such as (**30**) could reduce further ketone to give alcohol of opposite configuration to that produced by the catalyst, we replaced BMS with catecholborane (**31**), which has only one transferable hydride, and obtained a similar enantiomeric excess (24%, S-major, 83% yield) but at a considerably reduced rate (10 mol% (**29**), THF, rt, >98% reduction in 12 hrs). Some catalyst decomposition was also apparent using this reagent.



(30)



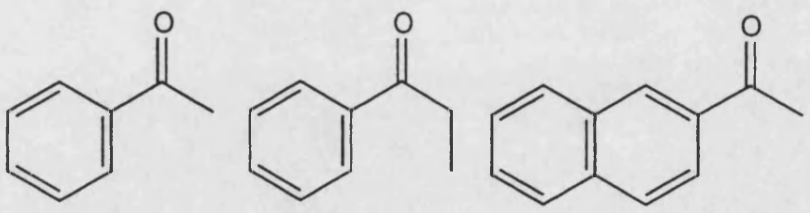
(31)

The use of monochloro borane (a more reactive source of hydride) gave, as expected, considerably lower selectivity (3% e.e., S-major, 71% yield) presumably due to competitive background reduction (10 mol% (**29**), THF, rt).

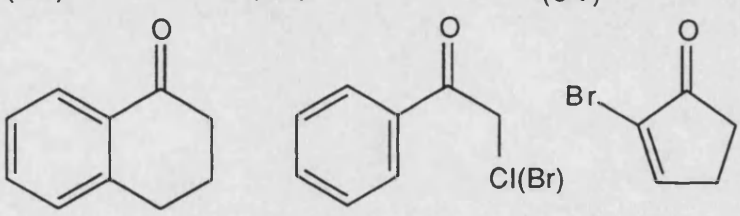
Slow addition of ketone to a solution of phosphinamide and borane in THF, an expedient known to be essential for good selectivity in a oxazaborolidine systems,[80,45] resulted in no change in selectivity. Both addition of borane to a solution of catalyst and ketone (the mode of addition used previously and throughout) and the reverse addition of ketone to a solution of catalyst and borane gave the same selectivity.

In all cases quantitative recovery of catalyst was possible *via* column chromatography and the recovered compound, which appeared spectroscopically identical to the original material, could be reused with no loss in catalytic activity, enantioselectivity or chemical yield of alcohol.

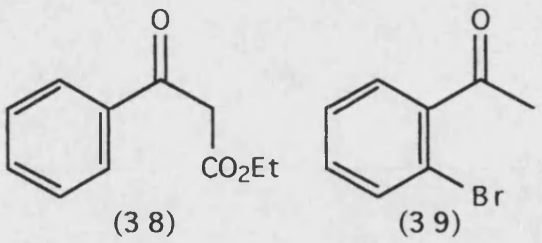
The reduction of ketones (**32**)-(**39**) was then examined using 10 mol% of phosphinamide (**29**) (Scheme 15, Table 2).

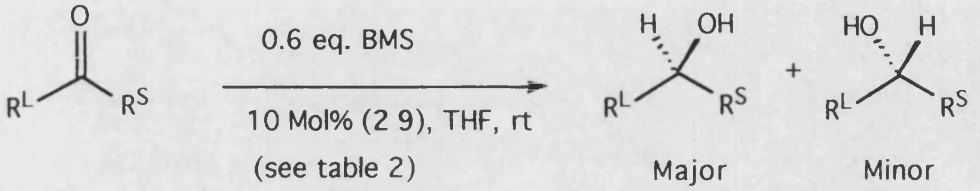


(32) (33) (34)



(35) (36) (37)





R^L = Large group (Ph, Ar, α-halo in (3 7)

R^S = Small group (Me, Et,CH_2Cl, CO_2Et)

Scheme (1 5)

Ketone	Mol% Catalyst (**29**)*	Time (>98% reduction)	Yield (isolated)	e.e.,**** (config.)
aceto-phenone (**32**)	10	< 1 hr	82%	26% (S)
(**33**)	10	<1 hr	88%	23% (S)
(**34**)	10	<1 hr	80%	30% (S)
(**35**)	10	<1 hr	97%	21% (S)
(**36**, **X=Cl**)	10	<1 hr	83%	22% (R)
(**36,X=Br**)	10	<1 hr	80%	25% (R)
(**37**)	10**	<1 hr	46%	46% (S)
(**38**)	10	<1 hr	80%***	5% (S)
(**39**)	10	<1 hr	91%	24% (S)

* 0.6 equivalents of BMS, THF (ca. 1M), ketone, rt.
** The reaction was carried out at 0 °C.
*** The diol was formed, see ref. 41.
**** The enantiometic excesses were measured by comparison of optical rotation with reported values, see ref. 42.

Table 2 Reduction of Ketones (**32**)-(**39**) Catalysed by (**29**).

Reduction of ketones (33)-(39) gave the corresponding alcohols with enantiomeric excesses similar to those obtained for acetophenone. The α-bromo enone (37) gave a product of slightly higher e.e. but in disappointing yield, while α-ketoester (38) was reduced to the diol in very low e.e.[41] In all cases the enantioselectivity appeared to be determined on the basis of size of ketone substituent[42] with hydride being delivered in the absolute sense illustrated in Scheme 15.

On this basis (38) would have been predicted to give the opposite enantiomer, however it is likely that in this case a competitive co-ordination with the ester group may have modified the borane reactivity.

The precise mechanism by which chiral information was transferred during the reduction is uncertain, though it seemed likely that the chiral centre in the side chain exerts a conformational effect on the two diastereotopic phenyl rings, which in turn exert a steric influence on the approach of the ketone to the phosphorus atom.

A single crystal X-ray structure of (29) was determined (Figure 10 and Appendix 1) which clearly showed the conformation of the phenyl rings with respect to the amide side chain, and a rehybridised sp^2 nitrogen atom implying good overlap between the nitrogen lone pair and the phosphorus atom. The ^{1}H-NMR spectrum of (29), however, showed no evidence of restricted rotation around the P-N bond even at low temperature.

Replacing phosphinamide (29) with triphenylphosphine oxide resulted in no acceleration of the reduction reaction. The nitrogen atom thus appeared essential for catalysis presumably due to its electron donating properties.

An encouraging observation was the apparent insensitivity of the catalyst to moisture, a problem in oxazaborolidine mediated reductions.[28] In an experiment in which one equivalent of water (relative to catalyst (29)) was added to a mixture of acetophenone and (29) prior to borane addition, the rate of reduction appeared uneffected, and a product of identical e.e. (26%, S-major, 85% yield) was obtained.

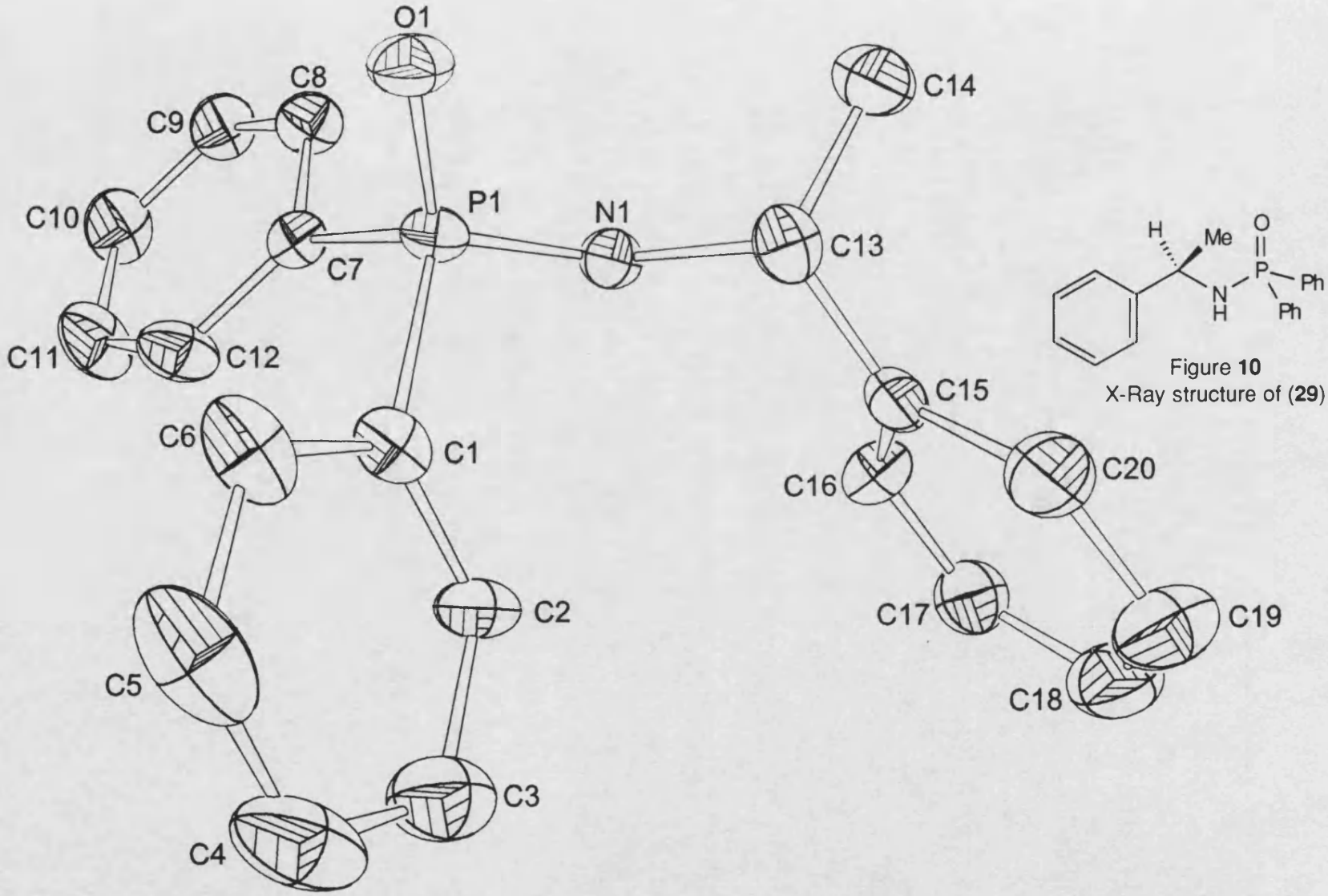
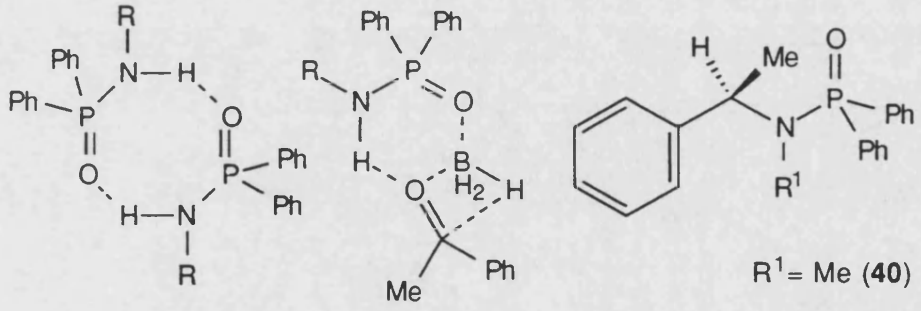


Figure **10**
X-Ray structure of (**29**)

Encouraged by these initial observations, and the apparent stability and robustness of the phosphinamide system to reaction conditions we began an investigation of the steric and electronic factors important for catalysis.

Section 2.2: Modification of Basic Phosphinamide Structure.

In order to confirm that a hydrogen bonding interaction between two molecules of (**29**) giving a dimeric species[43, 30a], or between catalyst and substrate was not a prerequisite for catalysis (Figure 11), we prepared compound (**40**) in 58% yield by N-methylation of (**29**) (*n*-BuLi, THF, MeI, rt), or in slightly higher yield by reaction of N-methyl-α methylbenzylamine[46] with diphenylphosphinic chloride (triethylamine, DCM, rt, 82% yield).



R = R-(+)-α methylbenzyl

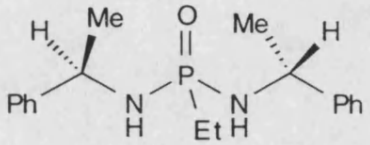
R^1 = Me (**40**)

Bn (**41**)

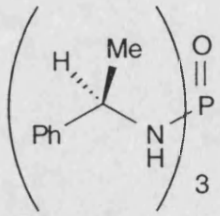
Figure 11

The presence of the methyl group appeared to have very little effect on the rate of catalysis (>98% reduction in < 2 hours at rt), and gave a product of 12% e.e. in favour of the S- enantiomer (90% yield) at a concentration of 10 mol%. The corresponding N-benzyl compound (**41**), prepared in 40% yield by alkylation of (**29**) under the above conditions, was a very poor catalyst for acetophenone reduction requiring some 3-4 hours for complete reaction and giving a racemic alcohol product, presumably due to a steric effect.

We next examined the effect of increasing the number of α methylbenzylamine groups bonded to phosphorus. Phosphonamide (**42**) was prepared from R-(+)-α methylbenzylamine and ethylphosphonic dichloride (triethylamine, DCM, rt) in 65% yield and the corresponding triamide (**43**) was prepared from phosphorus oxychloride under the same conditions in 80% yield. Both were crystalline solids, easily purified by flash chromatography and crystallisation. The use of these compounds for acetophenone reduction catalysis is summarised in Table 3.



(**42**)



(**43**)

Catalyst*	Mol% Catalyst	Temp.	Time (>98% reduction)	Yield (isolated)	e.e. (config.)
42	2	rt	< 1 hr	76%	26% (S)
42	10	rt	< 1 hr	88%	28% (S)
42	20	rt	< 1 hr	82%	33% (S)
42	2	0 °C	3 hrs	78%	35% (S)
43	10	rt	< 1 hr	70%	20% (S)

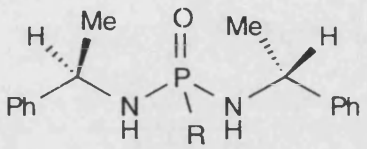
* 0.6 equivalents of BMS added to a 1M THF solution of ketone and catalyst.

Table 3 Reduction of Acetophenone catalysed by Phophonamides (**42**) and (**43**).

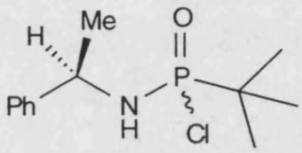
The results obtained were very similar to those obtained with (**29**) again suggesting a dominant catalyst mediated reduction pathway. Slightly better selectivity was obtained with the C_2 symmetric phosphonamide (**42**).

We next wished to examine the steric effect of the phosphorus substituent in phosphonamides structurally related to (**42**).

Phenyl- and *t*-butylphosphonic dichloride were prepared from the corresponding commercially available phosphonic acids using oxalyl chloride.[44] Reaction of phenylphosphonic dichloride with 2 equivalents of R-(+)-α methylbenzylamine (2 equivalents of triethylamine, DCM, rt) gave the phenyl substituted phosphonamide (**44**) in 45% yield. Reaction of *t*-butylphosphonic dichloride with the amine under the same conditions gave an inseparable 1.6:1 mixture of monochloro diastereoisomers (**48**) in 39% yield. Addition of the purified diastereomeric mixture (**48**) to a solution of lithiated α-methylbenzylamine (1.2 equivalents of amine, 1 equivalent of *n*-BuLi, THF, 0 °C) in THF gave the required *t*-butyl phosphonamide (**46**) in 81% yield.



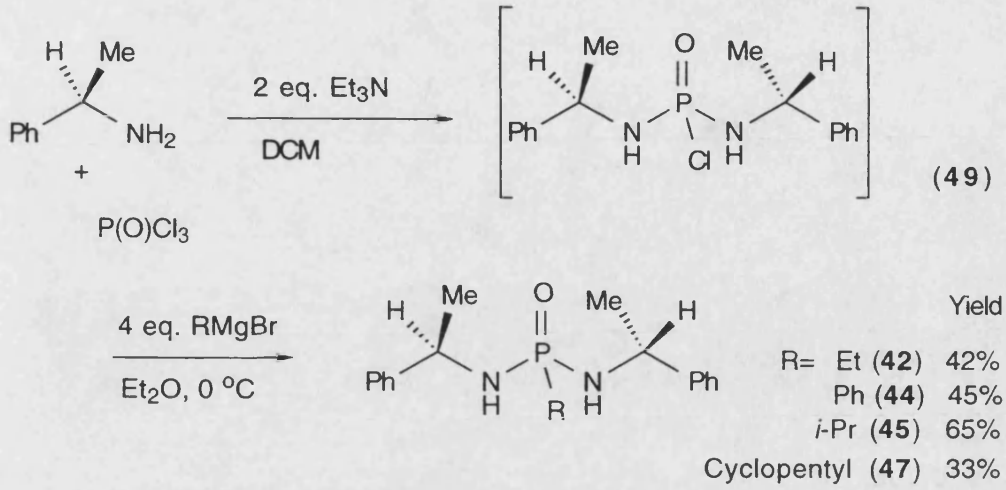
R= Ph (**44**)
R= *i*-Pr (**45**)
R= *t*-Bu (**46**)
R= Cyclopentyl (**47**)



(**48**)

Due to the lack of commercial availability of the requisite phosphonic acids, we required a more flexible synthetic route to these compounds. To this end we developed the synthetic sequence outlined in Scheme 16.

Addition of 2 equivalents of R-(+)-α methylbenzylamine to a dilute solution of phosphorus oxychloride in DCM gave the intermediate monochloride (**49**) as a viscous oil. Reaction of a diethyl ether solution of the unpurified chloride with 4 equivalents of the appropriate Grignard reagent[47] at 0 °C gave the required phosphonamides in good yield (Scheme 16).



Scheme **16**

A summary of the results obtained using the phosphonamide derivatives as catalysts for the reduction are shown below (Table 4).

R-group	Catalyst*	Mol% Catalyst	Temp.	Time >98% reduction	Yield (isolated)	e.e. (config.)
Ethyl	(**42**)	10	rt	< 1 hr	88%	28% (S)
Phenyl	(**44**)	10	rt	2 hrs	83%	30% (S)
Phenyl	(**44**)	2	rt	2-3 hrs	87%	18% (S)
Phenyl	(**44**)	2	-30 °C	6 hrs	40%	21% (S)
i-Propyl	(**45**)	8	rt	1-2 hrs	94%	50% (S)
t-Butyl	(**46**)	2	rt	2-3 hrs	83%	13% (S)
Cyclo-pentyl	(**47**)	10	rt	1-2 hrs	88%	15% (S)

* 0.6 equivalents of BMS added to a 1M THF solution of ketone and catalyst.

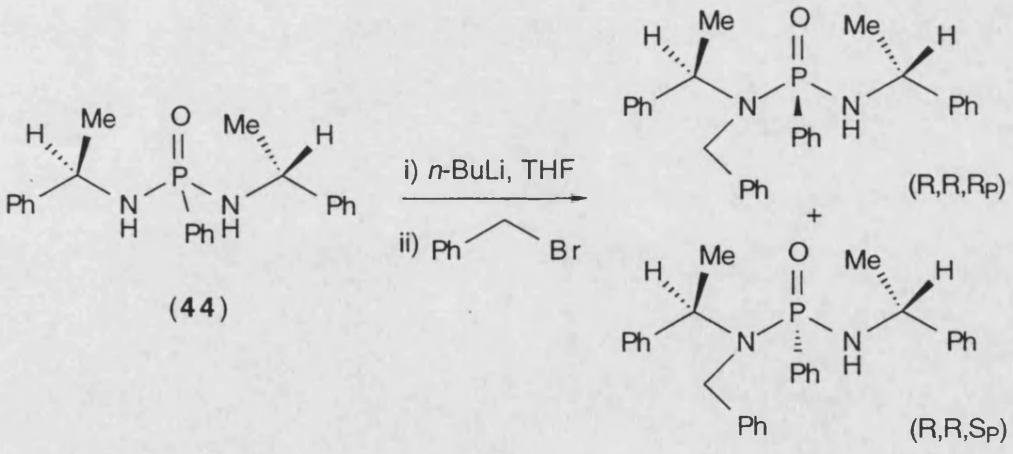
Table 4 Reduction of Acetophenone catalysed by C_2 symmetric phosphonamides.

All the compounds examined gave similar rates of catalysis (as assessed by TLC analysis). Phenylphosphonamide (**44**) gave slightly higher selectivity than the

corresponding ethyl- substituted analogue (**42**). Increasing the size of the phosphorus substituent from ethyl to isopropyl (**45**) gave a significant increase in selectivity, though the more sterically encumbered *t*-butyl compound (**46**) required a longer reaction time for complete reduction and gave an alcohol product of only 13% e.e. These results indicated that the isopropyl group was an optimal size for a substituent at this position.

At this stage all of the compounds we had examined were achiral at phosphorus. Since variation of the steric environment around the phosphorus centre appeared to have a significant effect on selectivity in the C_2 symmetric phosphonamide systems, we reasoned that introduction of a chiral environment at phosphorus, proximal to the reaction centre, either by desymmiterising the C_2 symmetric phosphonamides (**44**)-(**47**) or by replacing one of the diastereotopic phenyl groups in (**29**) with another group would give greater control of reduction facial selectivity.

To this end, phosphonamide (**44**) was treated with one equivalent of *n*-BuLi in THF at rt, and the resulting mono-anion quenched with benzyl bromide (Scheme 17).



Scheme **17** 41% (**50**)

This gave a 41% yield of the required epimers (**50**) as a 1:1 mixture. Attempts to separate the mixture by chromatography or crystallisation were

unsuccessful, though pure samples of each compound could be obtained by preparative TLC. The absolute configuration at phosphorus was not determined. The results obtained using these compounds is summarised below (Table 5).

Catalyst*	Mol% Catalyst	Temp.	Time (>98% reduction)	Yield (isolated)	% e.e. (config.)
44	2	rt	2.5 hrs	87 %	18 (S)
50U**	2	rt	2.5 hrs	89%	21 (S)
50L	2	rt	< 1 hr	81%	17 (S)

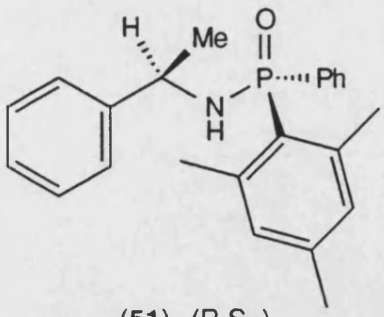
* 0.6 equivalents of BMS added to a 1M THF solution of ketone and catalyst.
** For convenience, the suffix U and L refer to epimer polarity; U being the less polar and L the more polar compound.

Table 5 Reduction of Acetophenone catalysed by (**50U**) and (**50L**).

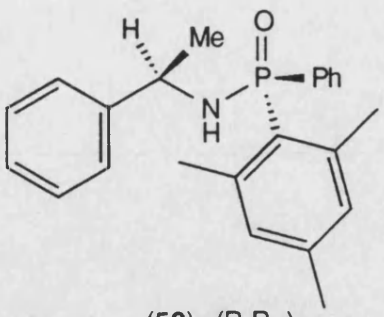
Both compounds appeared to give similar reduction enantioselectivity; the magnitude being similar to the C_2 symmetric phosphonamide (**44**). The more polar epimer (**50L**) did, however, appear to be a more active catalyst in terms of acceleration of the reaction with no ketone being present in the reaction mixture (by TLC) after 1 hour.

Since the presence of an N-benzyl substituent did not appear to have a significant effect on selectivity in the phenylphosphonamide system (derived from (**44**)), we attempted the same N-alkylation protocol with isopropyl phosphonamide (**45**). No alkylation was achieved under the previously used conditions (*n*-BuLi, THF, Benzyl bromide) presumably due to steric hindrance around the nitrogen atom. Repeating the reaction using methyl iodide as the alkylating agent gave the same result.

We next turned our attention to the diastereomerically pure phosphinamides (**51**) and (**52**).



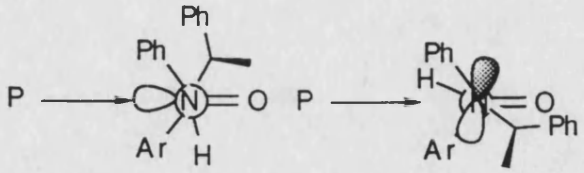
(**51**) (R,S_P)



(**52**) (R,R_P)

The preparation of these compounds had been reported by Jennings,[48] with the absolute configuration at phosphorus determined by single crystal X-ray diffraction of (**51**). Interestingly, the unit cell was found to contain two molecules which differ with respect to the conformation of the R_2N unit relative to the P=O bond. The molecule in which these are perpendicular contains an sp^3 hybridised nitrogen atom whilst the molecule in which they are close to planarity contains an essentially sp^2 hybridised nitrogen atom.

It would seem that the orientation of the lone pair electrons on the nitrogen atom relative to the P-O bond is not highly energy sensitive and that packing considerations may play an important role in determining the actual conformation about the P-N bond (Figure 13). Though caution should be exercised in the use of ground state structures to predict conformation in solution, we considered these observations significant since an electron rich P=O bond, we believed, was a prerequisite for effective activation of borane.



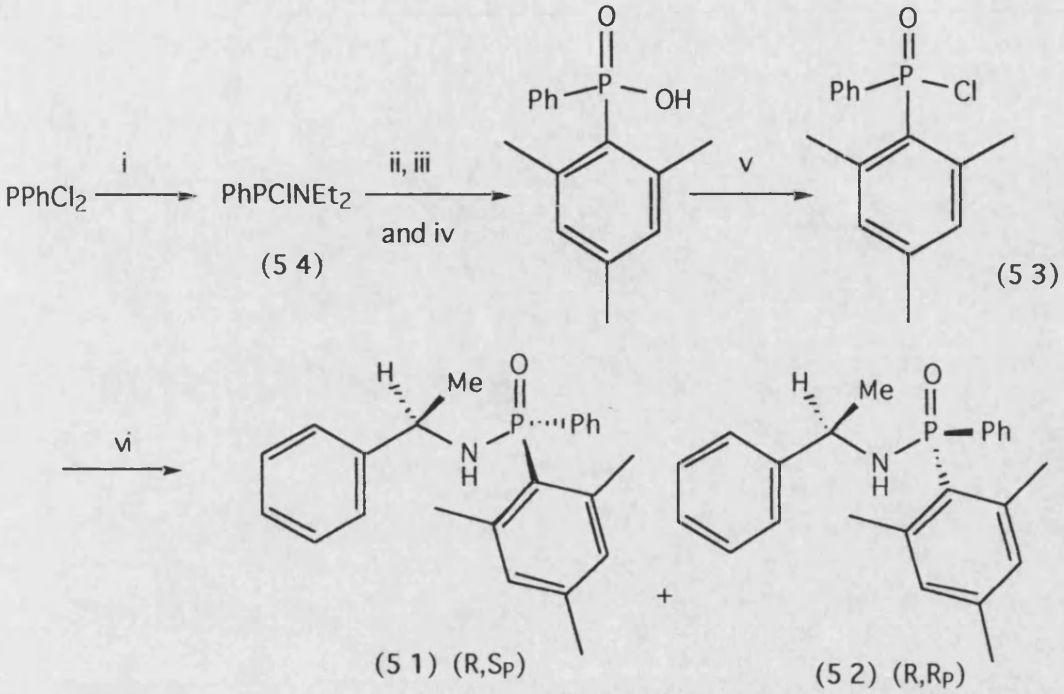
Molecule 1 in unit cell

Molecule 2 in unit cell

Figure **13**

Attempted preparation of these compounds *via* the route reported by Jennings proved problematic (Scheme 18). All attempts to prepare pure samples of

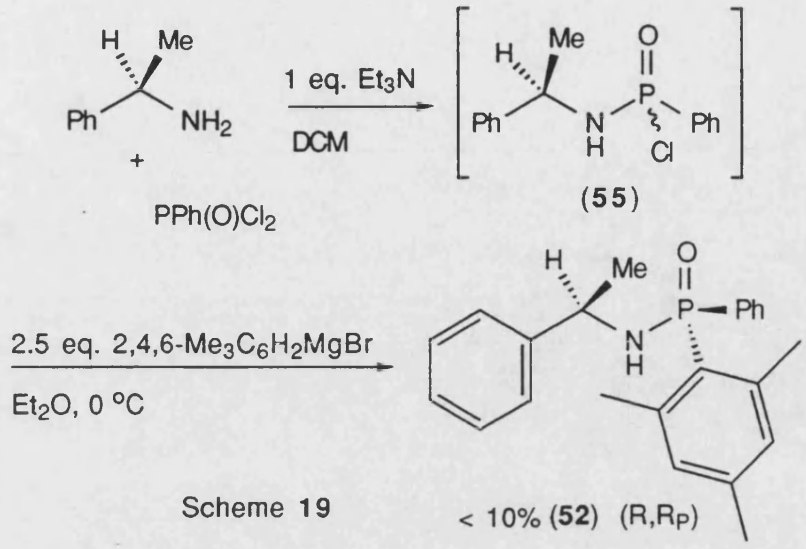
chloride (**53**) were unsuccessful, and difficulty in handling the aminophosphine (**54**) led us to examine another approach.



Reagents and conditions: i) $HNEt_2$, Et_2O, 0 °C, 2 hrs, rt overnight,62%; ii) 2,4,6-$Me_3C_6H_2MgBr$, Et_2O; iii) H_2O_2, acetone, reflux , 4 hrs; iv) conc HCl, 6 days, <30%; v) $SOCl_2$, reflux, 2 hrs, <10%; vi) R-(+)-αmethylbenzylamine, Et_3N Et_2O, rt overnight.

Scheme (1 8)

We found that addition of R-(+)-α methylbenzylamine to a very dilute solution of phenylphosphonic dichloride in DCM (1 equivalent of triethylamine, rt) gave mono-chloride (**55**) as a viscous oil. Reaction of a crude solution of the chloride in diethyl ether with 2.5 equivalents of mesitylmagnesium bromide gave, after chromatography and crystallisation, a low yield (<10%) of the R, R-diastereoisomer (**52**) as a white crystalline solid (Scheme 19). Assignment of the configuration at phosphorus was made by comparison of data with that reported by Jennings.[48]



Scheme 19

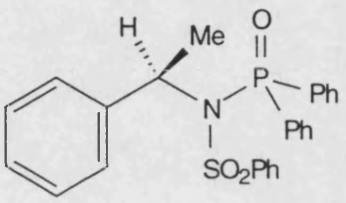
Use of 2 mol% of this compound under standard reduction conditions (Scheme 14) gave an alcohol product of 20% e.e. (S- major, 96% yield) with reduction being complete in 2-3 hours at rt. The selectivity obtained with (**52**) appeared similar to that obtained with phosphinamide (**29**); the increase in time required for complete reduction , we believed, reflecting the increase in steric crowding around the phosphorus atom. Unfortunately attempts to isolate the R, S-diastereoisomer (**51**) were unsuccessful.

It thus appeared that generation of a chiral environment around the phosphorus centre in the α methylbenzylamine derived catalysts had little effect on reduction selectivity, but appeared to effect the rate of ketone reduction. Rather than pursue this in an exhaustive series of studies, we moved on to examine other factors important for catalysis.

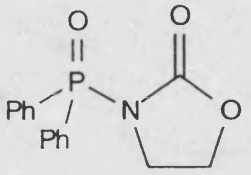
Section 2.3: Electronic Variation.

Our proposed catalyst cycle (Scheme 13) requires an electron rich P=O bond for initial donation and activation of the borane reagent. The nitrogen lone pair, though less involved in π- bonding to phosphorus than the corresponding carboxylic amides,[30] is important in that it increases electron density in the P=O bond

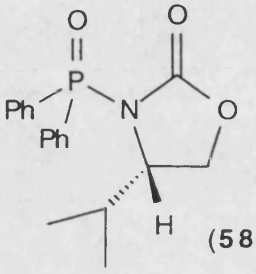
sufficiently to allow co-ordination to electrophilic borane. The importance of nitrogen π-bonding to phosphorus was next examined by introduction of an electron withdrawing group on the nitrogen atom. To this end we prepared compounds (**56**)-(**58**). The nitrogen lone pair in these compounds should be less involved in π-bonding to phosphorus due to conjugation effects.



(**56**)

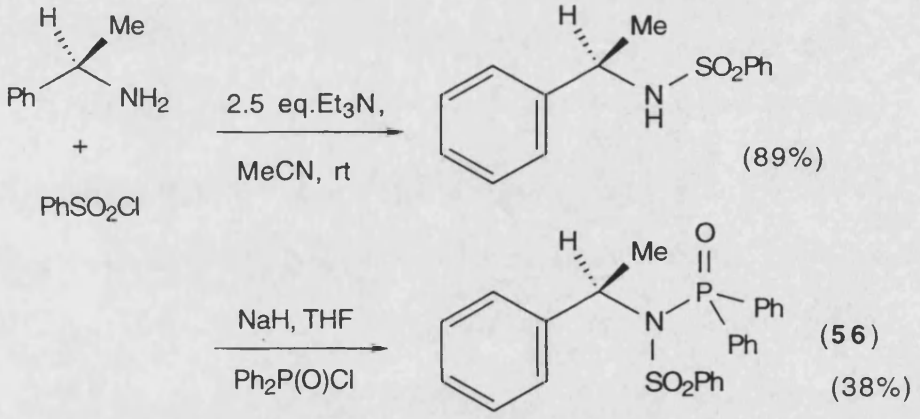


(**57**)



(**58**)

The N-sulfonyl phosphinamide (**56**) was prepared from the corresponding N-sulfonyl amine[49] and diphenylphosphinic chloride (sodium hydride, THF) in 38% yield (Scheme 20).

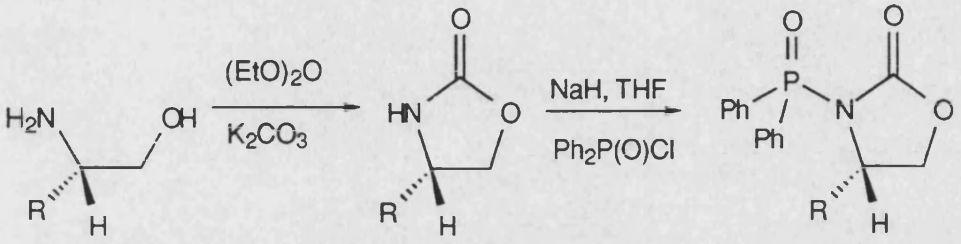


Scheme **20**

Gratifyingly, this compound appeared to show no catalytic activity; reduction of acetophenone requiring 10 hours at rt to go to completion and thus barely being distinguishable from the background reduction rate. The resulting alcohol was racemic.

Compounds (**57**)-(**58**) were prepared from the corresponding amino alcohols

as shown in Scheme 21. The requisite oxazolidinones were prepared according to a literature procedure using diethyl carbonate.[50] Addition of diphenylphosphinic chloride to the deprotonated oxazolidinone (sodium hydride, THF, rt) gave the phosphinamides as white crystalline solids in good yield.



R= H, 68%
i-Pr, 79%

R= H, (**57**) 73%
i-Pr, (**58**) 85%

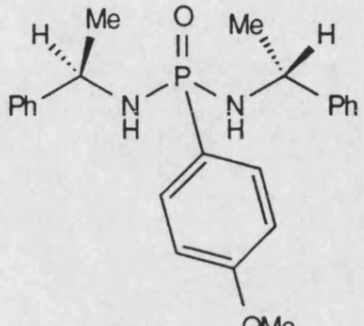
Scheme **21**

Phosphinamide (**57**) again appeared to show reduced catalytic activity; 10 mol% of this compound promoted >98% reduction of acetophenone in 3 hours at rt. The corresponding S-valinol derived compound (**58**) catalysed the reaction at a similar rate and gave an alcohol of 7% e.e. (R major, 84% yield).

These results suggested that electron withdrawing substituents on the nitrogen atom of the N-P=O system considerably reduced the rate of catalysis and hence enantioselectivity (presumably due to competitive background reduction). Donation of electron density from nitrogen to the phosphorus atom thus appeared important for catalysis. The possibility of a steric effect also being in operation could not, however, be neglected. Also co-ordination of borane to the sulfonyl oxygen in (**56**) and the carbamate carbonyl group in (**57**) and (**58**) could have a detrimental effect on borane reactivity, however both the carbamate and sulfonyl derivatives were found to be stable to the reagent.

We next examined the effect of an electron donating substituent on phosphorus, an expedient which should increase electron density in the P=O bond. Phosphonamide (**59**) was prepared by reaction of phosphorus oxychloride with two

equivalents of R-(+)-α methylbenzylamine (Triethylamine, DCM), followed by reaction of the resulting crude chloride (**49**) with p-methoxyphenylmagnesium bromide,[47] in 41% yield as described in Section 2.2 (Scheme 16).



(59)

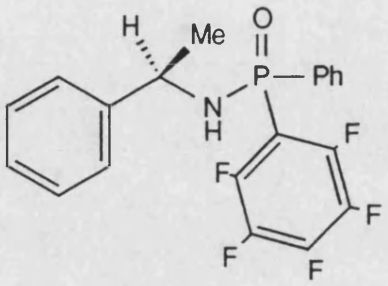
Remarkably, in the presence of 5 mol% of this compound, no acetophenone could be detected in the reaction mixture (by TLC) after 15 minutes at room temperature. Addition of BMS to a solution of phosphonamide and ketone produced a noticeable exothermic effect and gave the alcohol in 24% e.e. (S major, 90% yield).

We reasoned that the methoxy group significantly increases electron density in the P=O bond through conjugation effects resulting in increased donation and hence activation of borane (Scheme 13). It appeared that donation of electron density to borane was important for catalysis and this suggested that the donor properties of the phosphonamides were more significant than their acceptor properties. The extent of asymmetric induction did not, however, appear to be greatly effected; the result obtained being of the same magnitude as the unsubstituted phenyl phosphonamide (**44**).

To corroborate this idea we next investigated the effect of an electron withdrawing substituent on phosphorus, which should have a adverse effect on catalysis.

Phosphinamide (**60**) was prepared as a single diastereoisomer in 28% yield by reaction of phenylphosphonic dichloride with one equivalent of R-(+)-α

methylbenzylamine (1 equivalent of triethylamine, DCM) followed by reaction of crude chloride (**55**) with 2.5 equivalents of pentafluorophenylmagnesium bromide[51] as described in Section 2.2 (Scheme 19). The absolute configuration at phosphorus was not determined.



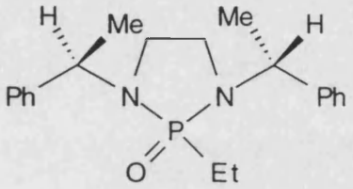
(**60**)

This compound did not appear to catalyse the reduction reaction; acetophenone was still present in the reaction mixture after stirring overnight at room temperature. Again we reasoned that the P=O bond in this compound should be less electron rich than the corresponding hydro- derivative (**29**) due to inductive withdrawal of electron density by fluorine. By the same argument as outlined above we would expect this compound to show little or no catalytic activity. Since the fluorine atom is isosteric with hydrogen we believed this to be a purely electronic effect.

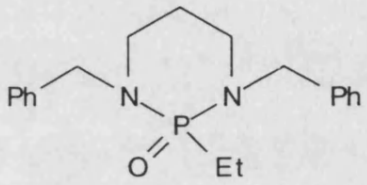
In summary, electron withdrawing substituents on the nitrogen atom of the N-P=O unit appeared to decrease both the rate of catalysis and reduction selectivity. An electron rich substituent bonded to phosphorus appeared to dramatically increase catalytic rate, but with little effect on selectivity, and conversely an electron withdrawing group on phosphorus had a detrimental effect on both rate of catalysis and enantiomeric induction.

Section 2.4: Conformationally Restricted Systems.

Having established the electronic requirements for effective catalysis, we turned our attention to the control of reduction selectivity. The acyclic compounds so far examined had given modest asymmetric induction due in part, we believed, to the conformational flexibility of these molecules. In order to probe the importance of the conformation of the R_2N-P=O unit in the catalytic process and improve asymmetric induction we prepared a series of compounds in which the conformational freedom of this subunit was restricted by 'locking' the phosphorus atom in a ring.



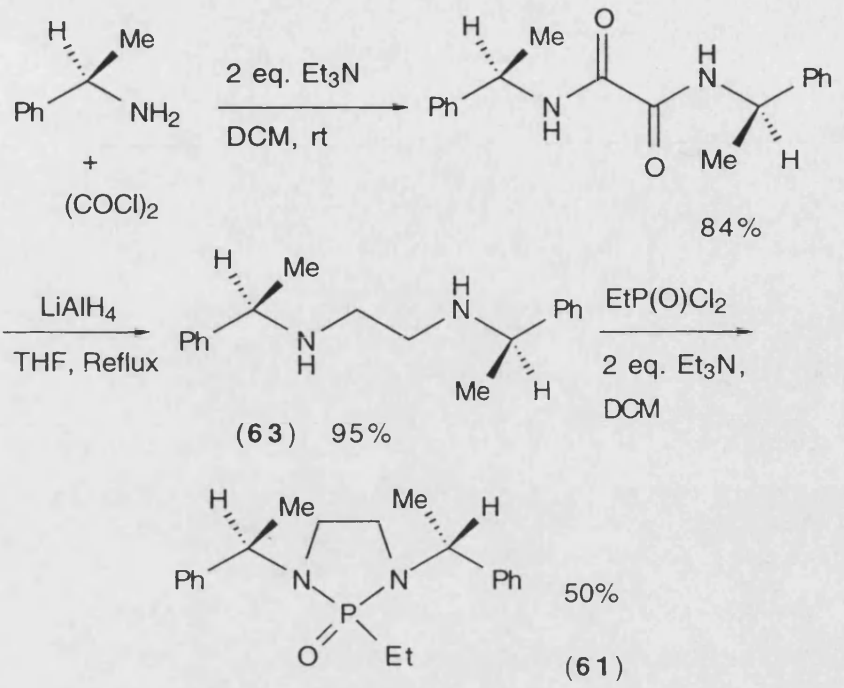
(61)



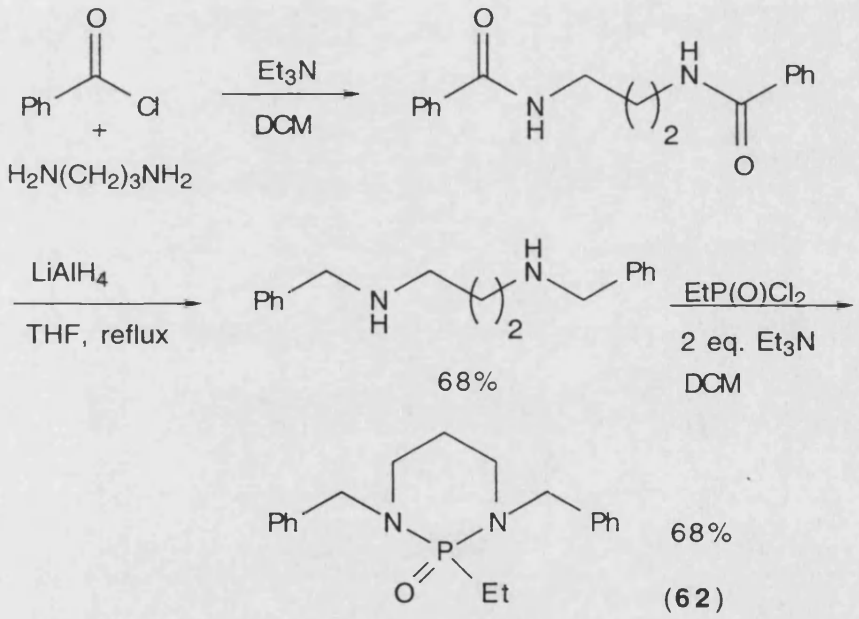
(62)

We first examined the effect of ring size on catalysis. To this end, cyclic phosphonamides (**61**) and (**62**) were prepared from the corresponding diamines *via* the method shown in Schemes 22 and 23.[52]

Reaction of R-(+)-α methylbenzylamine with oxalyl chloride (2 equivalents of triethylamine, DCM, rt) gave the *bis*-amide in 84% yield. Reduction of a refluxing THF solution of the amide using $LiAlH_4$ gave the corresponding diamine (**63**) in 95% yield.[61] Cyclisation of the diamine using ethylphosphonic dichloride (2 equivalents of triethylamine, DCM, rt) gave the phosphonamide (**61**) in 50% yield (Scheme 22). Similarly, reaction of benzoyl chloride with 1, 3-diaminopropane gave the crude *bis*-amide. Reduction of this material under the same conditions as above gave the diamine[115] in 68% yield which was cyclised with the dichloride giving phosphonamide (**62**) in 68% yield (Scheme 23).



Scheme **22**



Scheme **23**

Remarkably, both compound (**61**) and (**62**) proved to be poor catalysts for the reduction of acetophenone by borane; reaction times in excess of 5 hours being required for reduction. The results are summarised in Table 6.

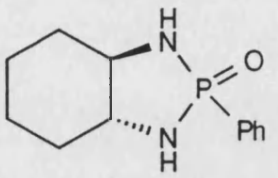
Catalyst*	Mol% Catalyst	Time (>98% reduction)	Yield (isolated)	e.e. (config.)
(42)	2	< 1 hr	88%	28% (S)
(61)	2	> 5 hrs	92%	2% (S)
(62)	2	> 5 hrs	88%	-
(64)	10	3 hrs	90%	4% (S)
(25)	10	4 hrs	85%	35% (R)

* 0.6 equivalents of BMS added to a 1M THF solution of ketone and catalyst at rt.

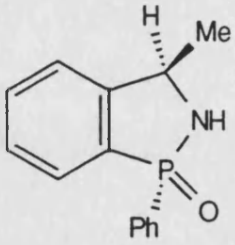
Table 6 Reduction of Acetophenone Catalysed by Conformationally Restricted phosphonamides.

The selectivity achieved using (**61**) was poor, again presumably due to competing background reduction. Comparison of the rate of catalysis with the corresponding acyclic phosphonamide (**42**) demonstrated a significant loss of activity with increased conformational rigidity. Similarly, the 6-membered ring analogue (**62**) proved incapable of accelerating the reaction.

We next examined the fused bicyclic phosphonamide (**64**),[117] prepared from the R, R-diamine and phenylphosphonic dichloride (2 equivalents of triethylamine, DCM) in 84% yield.



(64)



(R,Sp)

(25)

This compound again appeared to be a poor catalyst; a reaction time in excess of 3 hours being required for >98% reduction and the enantioselectivity was poor (Table 6).

Similar results were obtained using cyclic phosphonamide (**25**), prepared in

the Wills group by *ortho*-lithiation of the *t*-BDPS-protected amine,[53] in which the phosphonamide R_2N-P=O unit is locked in a five membered ring. This compound again appeared to be less effective at catalysis than the acyclic series of compounds (c.f. phosphinamide **29**)) though surprisingly gave an improved level of asymmetric induction (Table 6).

These observations suggested that the optimum geometry for catalytic activity is that in which the 'R_2N-P=O' system can lie in a single plane, thus maximising electron donation from the nitrogen lone pair to the P=O bond. This suggestion is supported by a number of X-ray structures in which nitrogen is shown to be sp^2 hybridised when this condition is satisfied, which implies a high degree of overlap[48,56] (Figure 14), allowing activation of borane followed by initiation of catalysis (Scheme 13). In contrast X-ray studies of compounds structurally related to (**64**), in which co-planarity cannot be attained, contain essentially sp^3 hybridised nitrogen atoms,[34,57] suggesting that electron donation to the P=O bond is a minimum (Figure 14).

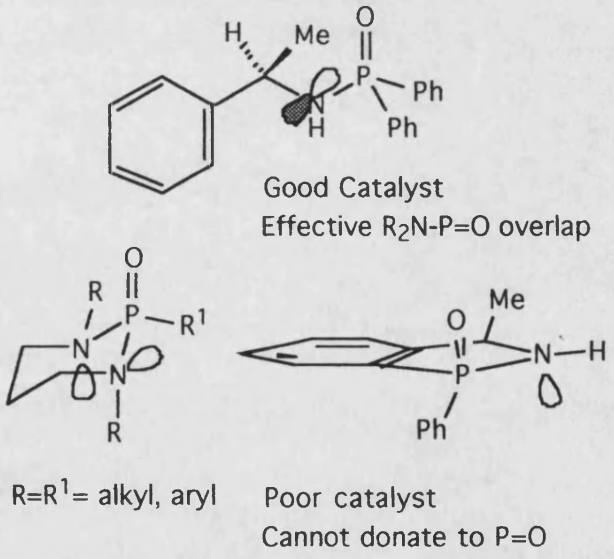


Figure 1 4

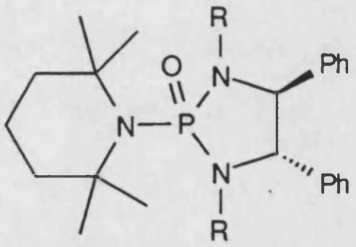
This interaction is, however, much weaker than the corresponding effect in carboxylic amides, and the energetic benefit can be outweighed by crystal packing

effects in some cases[48] (see the discussion of structure (**51**), Section 2.2). We reasoned that in compounds such as (**61**)-(**64**), which are poor catalysts, the co-planar geometry cannot be achieved, whilst in contrast the corresponding acyclic series of compounds (Section 2.2), which generate the highest acceleration in reduction rate, may readily achieve this.

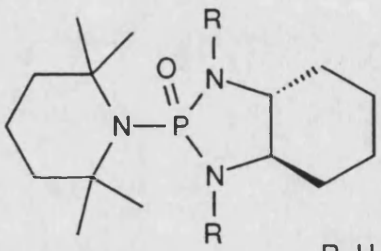
Section 2.5: Combined Donor Catalysts.

2.5.1 Triamides Derived from *C*2 Symmetric Amines.

At this stage we had established a clear stereoelectronic requirement for effective catalysis, but were still plagued by low reduction enantioselectivity. We believed that a conformationally restricted system was important for generation of a rigid chiral environment around the phosphorus atom, but needed to combine with this the characteristics of a 'fast' catalyst i.e good R_2N-P=O coplanarity. This, we believed, would go some way to improving enantioselectivity. These requirements are exemplified in structures of type (**65**)-(**66**).



(**65**)



R=H, alkyl

(**66**)

These molecules contain a sterically demanding exocyclic amine bonded to phosphorus which should, we believed, increase electron density in the P=O bond *via* π-bonding and prevent both borane complexation and ketone co-ordination in this region of the catalyst.

The ketone should co-ordinate with the phosphorus atom through its lone pair *trans* to the carbonyl phenyl group such that the bulky methyl group is oriented away from the sterically active ring phenyl group.

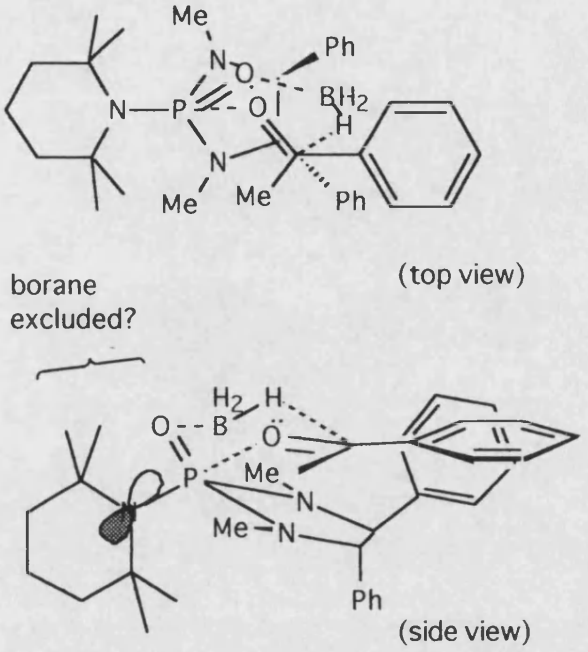
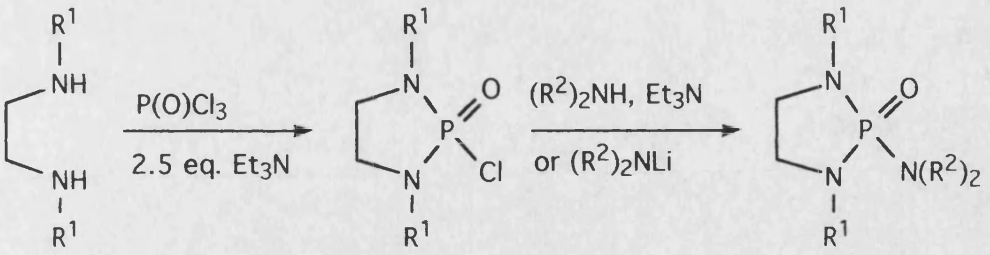


Figure 1 5
Proposed reduction transition state.

The conformationally locked C_2 symmetric[58] component thus creates a steric environment which can direct the orientation of ketone approach to phosphorus and hence facilitate enantiofacial differentiation (Figure 15). The method we proposed to employ in assembling these molecules is shown in Scheme 24.

Using this method, Alexakis has prepared a number of cyclic and bicyclic phosphoramidic chlorides[59] from C_2 symmetric diamines which have been employed as derivatising agents for the determination of the enantiomeric purity of both alcohols and amines.[60]



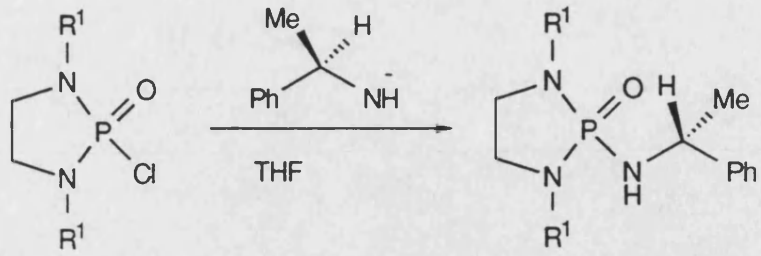
(6 7) (6 8)

R^1=R^2=alkyl

Scheme 2 4

In order to establish reaction conditions and the efficacy of this route we initially chose N, N'-dimethylethylenediamine (**67**, R^1=Me) as a 'model diamine' for the reaction. Reaction of phosphorus oxychloride with the diamine in refluxing toluene in the presence of triethylamine as reported by Alexakis[59,62] gave the corresponding chloride (**68**, R^1=Me) in 68% yield. Precipitation of amine hydrochloride salts during the reaction proved problematic and slowed the reaction considerably. We found that the procedure could be carried out more conveniently at room temperature in DCM (2.5 equivalents triethylamine) since the reaction mixture is homogeneous in this solvent. This gave the chloride (**68**, R^1=Me) in a reproducible 95% yield. The chloride appeared surprisingly stable and could be purified by chromatography and crystallisation without decomposition.

Attempted phosphinylation of R-(+)-α methylbenzylamine with chloride (**68**, R^1=Me) in DCM (2 equivalents of triethylamine, rt) was unsuccessful. Refluxing the mixture gave only decomposition products. Repeating the reaction in THF gave similar results, however, addition of a THF solution of the chloride to a solution of lithiated amine (1.2 equivalents *n*-BuLi, THF) in THF at 0 °C gave the required phosphoramide (**69**) in 68% yield (Scheme 25).



(68)

(69) R^1= Me, 68%

(70) R^1 = R-α methylbenzyl, 40%

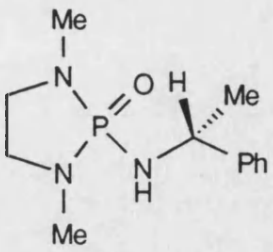
Scheme 25

Phosphoramide (**69**) was found to be a very effective catalyst for acetophenone reduction; 10 mol% giving complete reduction in <15 minutes at room temperature. and a reduction product of 17% e.e. (S major, 83% yield).

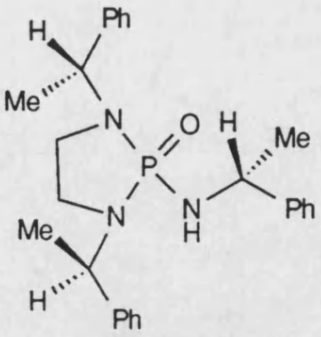
Having established a general procedure for preparation of the triamide catalysts and with the encouraging result above we began to implement a series of structural modifications.

Reaction of diamine (**63**) (prepared as described in Section 2.2.4)[61] with phosphorus oxychloride under our revised reaction conditions gave the corresponding chloride (**68**), R^1= R-α methylbenzyl) in 60% yield as a white crystalline solid (Scheme 24). Displacement of chloride with lithiated R-(+)-α methylbenzylamine occurred slowly at room temperature; unreacted starting materials being present after 2 days. Heating the mixture again resulted in decomposition of the chloride, presumably as a consequence of ring opening side reactions. Such anomalous reactions have been reported by Shapiro[63] and Johnson.[64] Steric crowding around the phosphorus atom may account for this lack of reactivity. As a result, phosphonamide (**70**) could only ever be obtained in 30-40% yield.

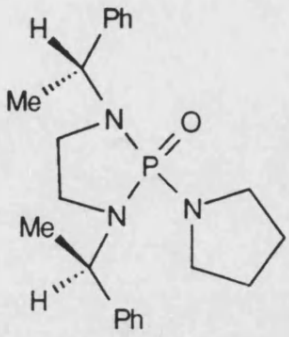
Reaction of a solution of chloride (**68**, R^1= R-α methylbenzyl) with 2 equivalents of pyrrolidine in DCM proceeded rapidly at room temperature giving triamide (**71**) in 48% yield. The more nucleophilic nature of the cyclic amine probably accounts for its increased reactivity.



(69)



(70)



(71)

Both compounds (**70**) and (**71**) were screened for catalytic activity. The results are summarised in Table 7 together with the results previously obtained for structurally related phosphonamide (**61**) and phosphoramide (**43**) (see Section's 2.4 and 2.2 respectively).

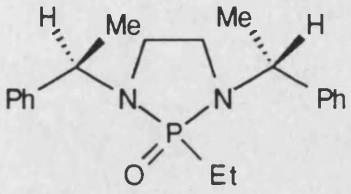
Catalyst*	Mol% Catalyst	Time (>98% reduction)	Yield (isolated)	e.e. (config.)
(43)	10	< 1 hr	70%	20% (S)
(61)	2	> 5 hrs	92%	2% (S)
(70)	10	2.5 hrs	89%	racemic
(71)	5	2.5 hrs	91%	5% (R)

* 0.6 equivalents of BMS added to a 1M THF solution of ketone and catalyst at rt.

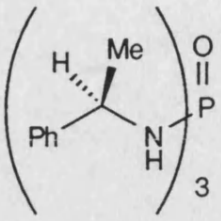
Table 7 Reduction of Acetophenone catalysed by (**70**) and (**71**).

Phosphoramide (**70**) appeared to accelerate the reduction but gave no chiral induction, presumably due to the steric effect of the large nitrogen substituent preventing ketone co-ordination (the corresponding N-methyl analogue (**69**) gave modest selectivity at a considerably increased rate). Replacement of the exocyclic α methylbenzyl unit with pyrrolidyl again resulted in low selectivity (the product alcohol being of R configuration) with reduction occurring at a similar rate.

Despite disappointing selectivity, the presence of the exocyclic amide bond did appear to increase the rate of catalysis relative to cyclic phosphonamide (**61**), though not as effectively as the conformationally less rigid phosphoramide (**43**).

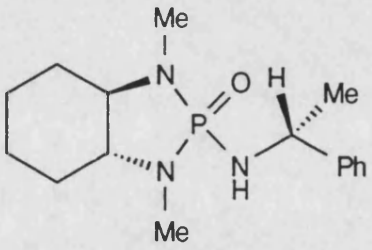


(61)



(43)

Since it appeared that the size of the nitrogen substituent in (**70**) had a detrimental effect on selectivity, we turned our attention to bicyclic phosphoramide (**72**) in which the chiral centres are in the backbone of the C_2 symmetric bicyclic framework.

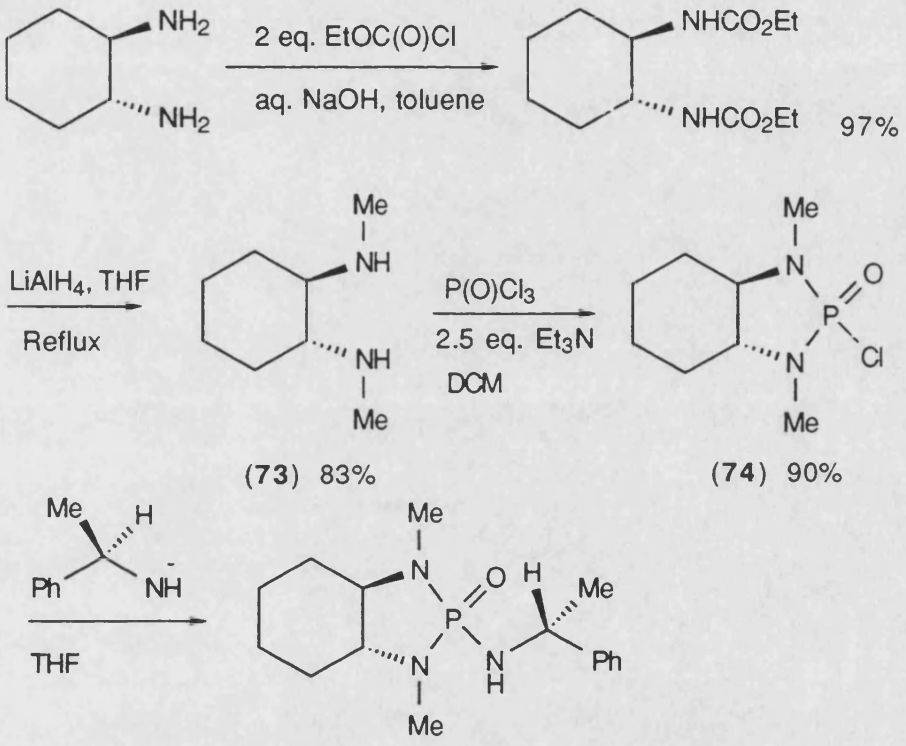


(72)

The synthesis of this compound was achieved as outlined in Scheme 26. Initially the synthesis was carried out using racemic diamine since it was hoped that separation of the resulting diastereoisomers would be possible, but unfortunately all attempts were unsuccessful.

In order to determine if the bicyclic triamide structure exhibited the required catalytic activity, a sample of the diastereomeric mixture prepared from racemic phosphoramidic chloride (**74**) (i.e. a 1:1 mixture of R, R, R and S, S, R-diastereoisomers) was screened in the reduction reaction. Remarkably the mixture

appeared to be extremely effective at mediating the reduction of acetophenone; all ketone being consumed in under 15 minutes at room temperature and giving an alcohol product of 30% e.e. (S major, 87% yield) (Table 8). Since each diastereoisomer could give opposite face selectivity in the reduction, pure R, R, R-diastereoisomer (**72**) was prepared from commercially available R, R-diaminocyclohexane as outlined in Scheme 26.

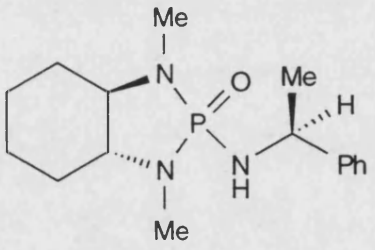


Scheme (**26**)

Reaction of the diamine with ethyl chloroformate in toluene gave the *bis*-carbamate in 97% yield. Reduction of a refluxing THF solution of the carbamate using $LiAlH_4$[65] gave the N, N'-dimethyl diamine (**73**) in 83% yield. Cyclisation of the pure R, R-dimethyl diamine with phosphorus oxychloride (2.5 equivalents of triethylamine, DCM) gave the corresponding phosphoramidic chloride (**74**) in 90% yield. Reaction of a THF solution of chloride (**74**) with lithiated R-(+)-α methylbenzylamine (1.2 equivalents of amine, 1 equivalent of *n*-BuLi, THF) in THF

gave the required R, R, R-diastereoisomer (**72**) in 44% yield. Problems were encountered in the displacement step due to competitive reaction of lithium *n*-butoxide (presumably present in the *n*-BuLi) with the electrophile; the product of which proved difficult to separate from the requisite triamide. This problem could be partially alleviated by using fresh butyllithium.

Triamide (**72**) appeared to give considerably lower selectivity and required a longer reaction time than the diastereomeric mixture (1 hour, 8% e.e., R major, 82% yield). The resulting alcohol was also of opposite configuration (Table 8). Assuming no synergic effects were in operation, we reasoned that the pure S, S, R-diastereoisomer should give the S-enantiomer of alcohol in high selectivity. Since the S, S-diamine is less readily available than the R, R- form, we prepared the enantiomer of the more active component of the mixture (i.e. the R, R, S-diastereoisomer (**75**)) in 36% yield *via* reaction of chloride (**74**) with lithiated S-(-)-α methylbenzylamine (1.2 equivalents of amine, 1 equivalent of *n*-BuLi, THF) in THF.



(**75**)

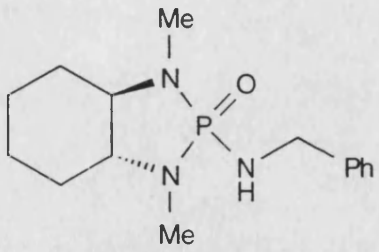
As predicted 10 mol% of this compound catalysed the reduction of acetophenone, with complete reduction occurring in less than 10 minutes at room temperature, and gave an alcohol of 46% e.e. (R major, 84% yield) (Table 8).

Catalyst*	Config.	Time (>98% reduction)	Yield (isolated)	e.e. (config.)
1:1 mixture	RRR, SSR	< 15 min	87%	30% (S)
(**72**)	RRR	1 hr	82%	8% (R)
(**75**)	RRS	<10 min	84%	46% (R)
(**76**)	RR	30 min	88%	19% (R)

* 0.6 equivalents of BMS added to a 1M THF solution of ketone and 10 mol% catalyst at rt.

Table 8 Reduction of Acetophenone Catalysed by Triamides Derived From Phosphoramidic Chloride (**74**).

It thus appeared that the diamine component of the system was directing the reduction to give alcohol of R configuration and that the directing influence of the α methylbenzyl group was either matched (in the case of the S- amine) or mismatched (in the case of the R-amine) with this diamine directing effect. With the R, R, S-diastereoisomer (**75**) both these effects are matched resulting in higher selectivity and increased rate of reduction (46% e.e., < 10 min.). In contrast, with the R, R, R-diastereoisomer (**72**), these effects essentially oppose one another resulting in reduced catalytic activity and lower selectivity (8% e.e., 1hr).

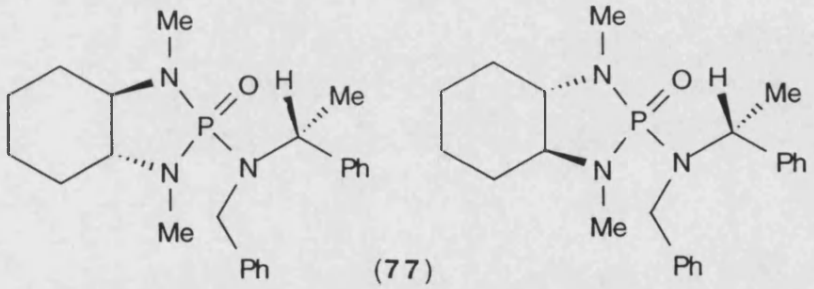


(**76**)

In order to confirm that the exocyclic amide side chain was having a controlling effect, phosphoramide (**76**) was prepared in 55% yield by reaction of chloride (**74**) with lithated benzylamine (1.2 equivalents of amine, 1 equivalent of *n*-

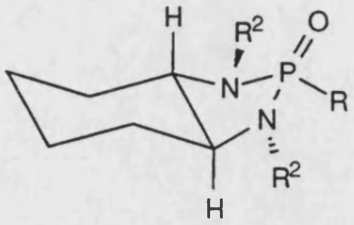
BuLi, THF) in THF. Repeating the reaction using this material as catalyst resulted in complete reduction of ketone in 30 minutes at room temperature and gave an alcohol product of 19% e.e. (R major, 88% yield) (Table 8). This result also demonstrated that the diamine component was giving the predicted R-selectivity in the reduction reaction.

Since in the acyclic phosphinamide series (Section 2.2) a large nitrogen substituent appeared to prevent ketone approach to phosphorus, we reasoned that this effect could be utilised to our advantage in 'amplifying' diamine control of reduction selectivity by directing ketone approach 'over' the rigid bicyclic ring system. To this end we prepared triamide (**77**) as a 1:1 mixture of R, R, R and S, S, R-diastereoisomers in 42% yield by N-benzylation of the primary amide mixture (*n*-BuLi, THF, benzyl bromide). Unfortunately the mixture did not show any catalytic activity and the resulting alcohol was racemic.



(77)

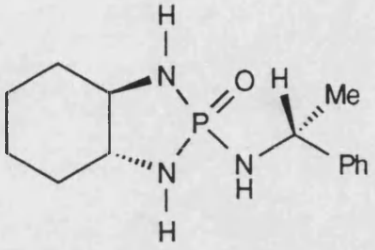
In the solid state structure of bicyclic phosphonamides such as (**64**)[57,66] the nitrogen substituents (R^2) are *syn* to the axial cyclohexyl protons and thus *anti* to each other and as a result the nitrogen substituents (R^2) act to project the chirality of the cyclohexyl carbon closer to the reaction centre (Figure 16).[65b,74] Since the nitrogen substituents are proximal to the reaction centre, we reasoned that the size of this substituent should have an effect on the efficiency of 'chirality transfer'. To examine this effect we wished to prepare the corresponding N-H phosphoramide series (**78**)-(**79**).



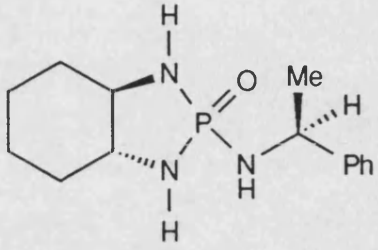
R = alkyl, aryl

R^2= alkyl

Figure 16

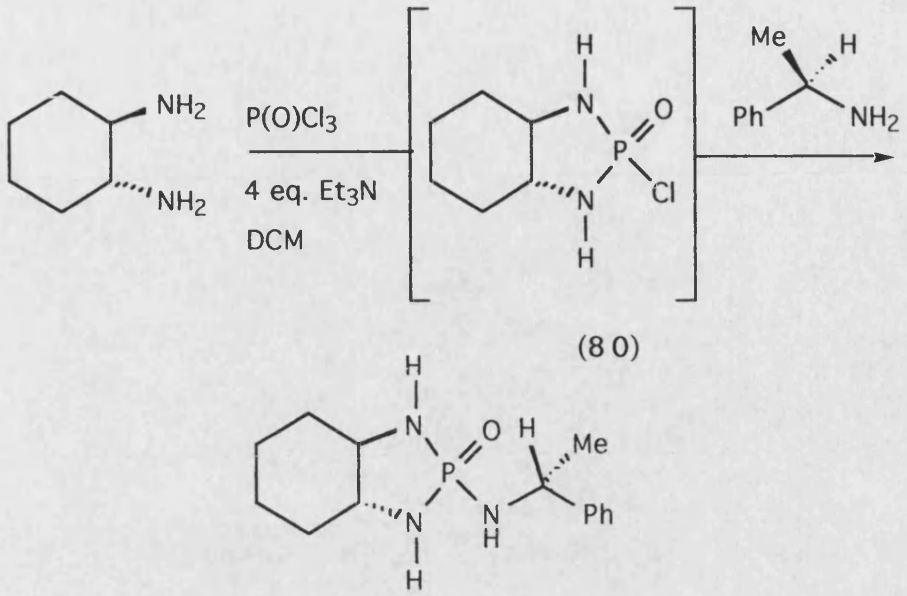


(78)



(79)

Addition of R, R-diaminocyclohexane to a dilute solution of phosphorus oxychloride in DCM (4 equivalents of triethylamine) gave the corresponding chloride (**80**). Attempted isolation of this material resulted in decomposition and formation of baseline material by TLC, however, *in situ* generation and trapping with R-(+)-α methylbenzylamine gave the required triamide (**78**) in 41% yield (Scheme 27). For direct comparison with the N-Me analogues, the corresponding R, R, S-diastereoisomer (**79**) was prepared in 40% yield via the same protocol using S-(-)-α methylbenzylamine. The results obtained using these compounds as reduction catalysts are summarised in Table 9 together with the N-methyl series for direct comparison.



(8 0)

(7 8), 41% Scheme 2 7

Nitrogen substituent	Catalyst**	Config.	Time (>98% reduction)	yield (isolated)	e.e. (config.)
H	(**78**)	RRR	< 30 min	89%	6% (R)
H	(**79**)	RRS	< 30 min	85%	11% (R)
H*	1:1 mixture	RRR+SSR	< 30 min	83%	8% (S)
Me	(**72**)	RRR	1 hr	82%	8% (R)
Me	(**75**)	RRS	< 10 min	84%	46% (R)
Me	1:1 mixture	RRR+SSR	<15 min	87%	30% (S)

* prepared in 25% yield using racemic chloride (**80**) (Scheme 27).
** 0.6 equivalents of BMS added to a 1M THF solution of ketone and 10 mol% catalyst at rt.

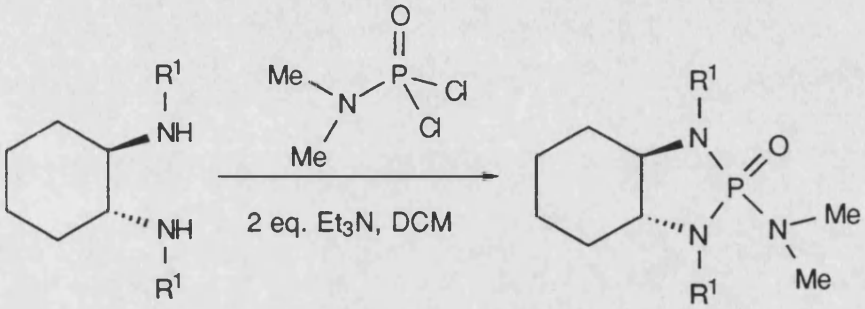
Table 9 Reduction of Acetophenone Catalysed by Triamides Derived from *In Situ* Generated Chloride (**80**).

The results obtained showed the same trends as the methyl series. It appeared that replacing the methyl group with hydrogen had little effect on rate of catalysis though it had a detrimental effect on selectivity. This, we presumed, was due to hydrogen being less effective at projecting chirality from the cyclohexyl

carbon than the more sterically demanding methyl group.

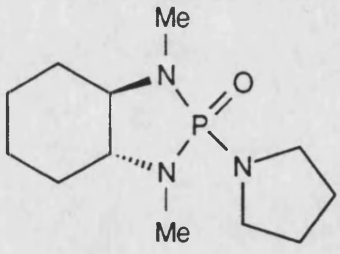
From our work on the simple triamide structures such as (**70**) we believed that increasing the size of the nitrogen substituent would not be worthwhile since it appeared to have a detrimental effect on catalyst turnover rate in these systems resulting in lower reduction enantioselectivity (c.f. phosphoramides (**69**) and (**70**)).

Since the majority of systems we had examined at this stage contained a primary exocyclic amide we turned our attention to the corresponding secondary amide series. Compounds (**81**)-(**82**) were prepared by reaction of the appropriate amine with N, N-dimethylphosphoramidodichloridate (2 equivalents of triethylamine, DCM) as shown in Scheme 28.



(**81**), R^1=H, 40%
(**82**), R^1=Me, 38%

Scheme **28**



(**83**)

Phophoramide (**82**) could also be prepared in better yield (58%) by methylation of the *bis*-anion of (**81**) (2.2 equivalents of *n*-BuLi, THF, rt then MeI)[73] or by reaction of chloride (**74**) with dimethylamine generated *in situ* by addition of triethylamine to a solution of the hydrochloride salt (2 equivalents of

triethylamine, DCM, rt, 53% yield). The pyrrolidine derived triamide (**83**) was prepared from chloride (**74**) in 84% yield (2 equivalents of pyrrolidine, DCM, rt). The results obtained using these compounds as reduction catalysts is summarised in Table 10.

Nitrogen substituent	Catalyst*	Time (>98% reduction)	yield (isolated)	E.e. (config.)
H	(**81**)	90 min	90%	10% (R)
Me	(**82**)	2 hrs	88%	3% (R)
Pyrollidyl	(**83**)	30 min	89%	2% (R)

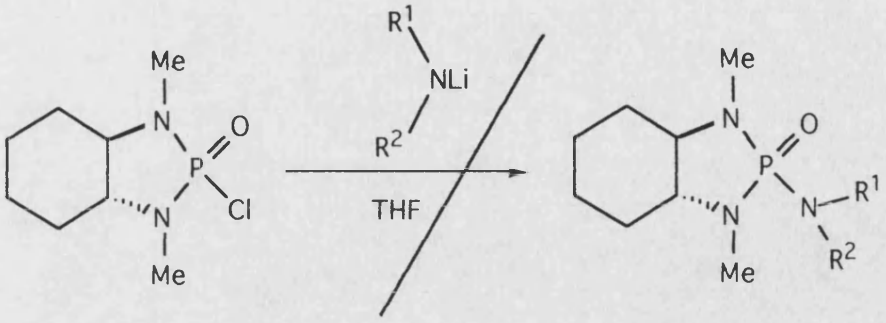
* 0.6 equivalents of BMS added to a 1M THF solution of ketone and catalyst in at rt.

Table 10 Reduction of Acetophenone Catalysed by Triamides (**81**)-(**83**).

These results showed that a secondary exocyclic amide bond appeared to lower selectivity, though again the rate of catalysis appeared virtually unaffected by this expedient. Unlike the previous examples, however, the N-H derivative (**81**) appeared to give marginally better selectivity than the corresponding N-Me compound (**82**). This, we believed, was due to the increased steric crowding in (**82**) hindering ketone approach to the phosphorus atom. The pyrrolidyl compound (**83**) gave a disappointingly low selectivity (2% e.e., 89% yield).

We next wished to examine the effect of introducing a more hindered secondary exocyclic amide bond. Attempted reaction of chloride (**74**) with hindered secondary amines such as diisopropylamine and 2, 2, 6, 6-tetramethylpipiridine proved unsuccessful, as did reaction of the corresponding lithium amides (1.2 equivalents of amine, 1 equivalent of *n*-BuLi, THF),[67] presumably due to steric effects and the inherent lack of nucleophilic character associated with hindered lithium amides (Scheme 29). The same lack of reactivity was observed with hindered primary amines such as *t*-butylamine and *i*-propylamine and their lithium

amide derivatives (Scheme 29). Attempted reaction of *in situ* generated chloride (**80**) with hindered primary and secondary amines also proved unsuccessful.



(7 4)

$R^1 = R^2$ = tetramethylpiperidyl

$R^1 = R^2$ = *i*-propyl

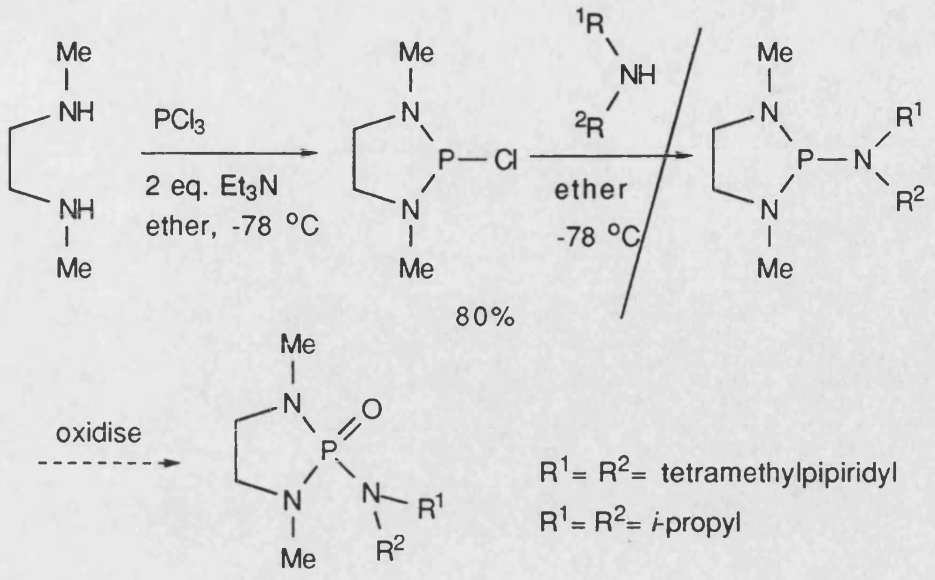
R^1 = H, R^2 = *t*-butyl

Scheme 2 9 R^1 = H, R^2 = *i*-propyl

Reaction of the appropriate N, N-dialkylphosphoramidodichloridate with the diamine gave a possible route to these derivatives (Scheme 28), however, preparation of the hindered dichloridates proved unreliable.[71]

Clearly another strategy for the assembly of these structures was required. The corresponding chloroaminophosphines[68] are considerably more reactive to nucleophiles than their phosphorus (V) counterparts and we next examined the route outlined in Scheme 30.

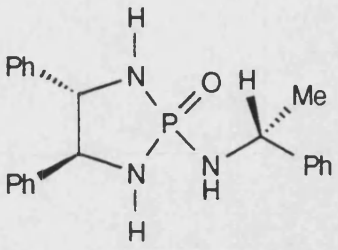
Reaction of N, N'-dimethylethylene diamine with phosphorus trichloride in diethyl ether at -78 ^{o}C (2 equivalents of triethylamine) gave the chloride in 80% yield.[69,70] Addition of a diethyl ether solution of 2, 2, 6, 6-tetramethylpiperidine to a diethyl ether solution of the chloroaminophosphine at -78 ^{o}C followed by warming to room temperature gave only decomposition products. The same result was obtained using diisopropylamine.



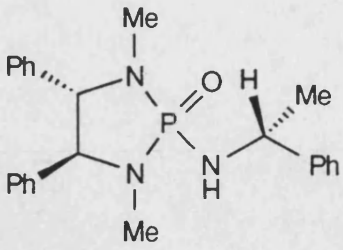
Scheme **30**

It thus appeared that preparation of these very hindered systems was not easily achieved and we became concerned that the phosphorus atom in these triamides may be too hindered to allow ketone co-ordination to phosphorus. The results obtained with both the dimethyl (**82**) and the pyrrolidyl (**83**) derivatives and the benzylated triamide (**77**) suggested this may indeed be the case. We therefore abandoned further attempts to prepare examples of this structural series.

We next decided to modify the conformationally locked C_2 symmetric 'backbone' of the phosphonamide ring system by replacing the cyclohexyl group with a *trans*-diphenyl arrangement as in triamides (**84**) and (**85**). This, we hoped, would aid transfer of 'chiral information' (possibly *via* a nitrogen substituent relay effect as described previously); the sterically demanding phenyl rings directing ketone approach. In this case the large groups are remote from the reaction centre which should, we hoped, prevent unfavourable steric crowding around the phosphorus atom.

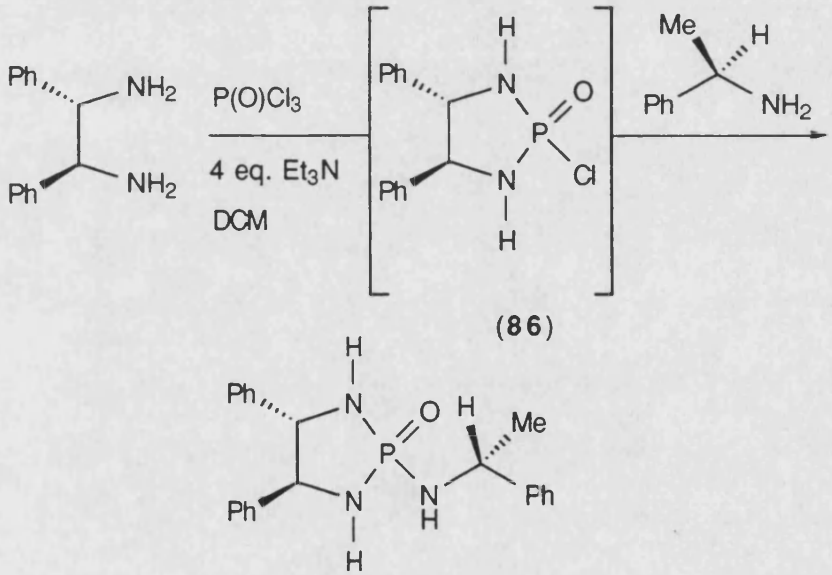


(84)



(85)

Phosphoramide (**84**) was prepared using the previously outlined procedure (Scheme 31). Addition of S, S-diphenylethylene diamine[72] to a dilute solution of phosphorus oxychloride in DCM (4 equivalents of triethylamine) gave chloride (**86**) *in situ* which was trapped with R-(+)-α methylbenzylamine to give the triamide (**84**) in 64% yield.



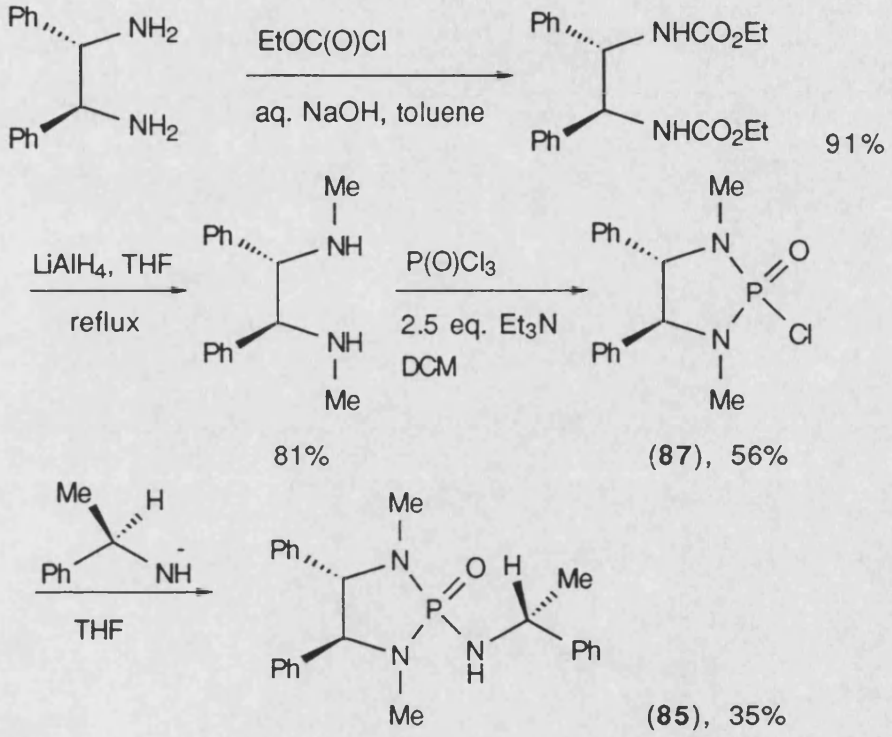
(86)

(84), 64%

Scheme **31**

The corresponding N-methyl derivative (**85**) was again prepared *via* a previously described route (Scheme 32). Reaction of S, S-diphenylethylene diamine with ethyl chloroformate in toluene gave the *bis*-carbamate in 91% yield. Reduction of a refluxing THF solution of the carbamate using $LiAlH_4$[65] gave the N, N'-dimethyl diamine in 81% yield. Cyclisation of the diamine with phosphorus

oxychloride (2.5 equivalents of triethylamine, DCM) gave the corresponding phosphoramidic chloride (**87**) in 56% yield. Reaction of a THF solution of chloride (**87**) with lithiated R-(+)-α methylbenzylamine (1.2 equivalents of amine, 1 equivalent of *n*-BuLi, THF) gave the required S, S, R-diastereoisomer (**85**) in 35% yield.



Scheme **32**

The results obtained using these compounds as catalysts for acetophenone reduction are summarised in Table 11 (together with those obtained for the cyclohexyl series for comparison).

Nitrogen substituent	Catalyst*	Config.	Time (>98% reduction)	Yield (isolated)	e.e. (config.)
H	(**84**)	SSR	< 10 min	87%	39% (S)
Me	(**85**)	SSR	45 min	81%	23% (S)
H	(**79**)	RRS	< 30 min	85%	11% (R)
Me	(**75**)	RRS	<10 min	84%	46% (R)

* 0.6 equivalents of BMS added to a 1M THF solution of ketone and 10 mol% catalyst at rt.

Table 11 Reduction of Acetophenone catalysed by triamides (**84**) and (**85**).

The *trans*-diphenyl system appeared to give an opposite trend to the corresponding cyclohexyl derivatives, (**79**) and (**75**), in that reduction rate and selectivity appeared to be higher with a primary bicyclic amide (**84**) relative to methylated analogue (**85**). This, we believed, was due to the enhanced long range projection of chirality from the axially disposed phenyl groups; the smaller nitrogen substituent resulting in less steric crowding around the phosphorus atom. The S, S-configuration of the diamine, by analogy with the cyclohexyl system, would be expected to direct the reduction to give S-stereochemistry and hence be matched with the propensity of the R-α methylbenzyl exocylic amide to give S-alcohol product. We did not, therefore, consider it worthwhile to screen the S, S, S-diastereoisomer series.

At this stage we had obtained a detailed structure activity relationship for the triamide catalysts and a summary of all the results is shown in Table 12 (Figure 17).

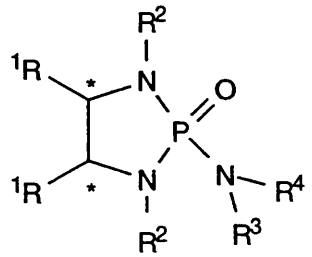


Figure 17

Table 12 Summary of the results Obtained for the Reduction ofAcetophenone Catalysed by Structurally Related Triamides.

Cat.*	R^1 ***	R^2	R^3	R^4	Time >98% redn	Yield isolated	e.e. config.
(69)	H	Me	H	R-α-MeBn	<15 min	83%	17% (S)
(70)	H	R-α-MeBn	H	R-α-MeBn	2.5 hrs	89%	racemic
(71)**	H	R-α-MeBn	--pyrrolidyl--		2.5 hrs	91%	5% (R)
(78)	R,R-cyhex.	H	H	R-α-MeBn	<30 min	89%	6% (R)
(79)	R,R-cyhex.	H	H	S-α-MeBn	<30 min	85%	11% (R)
(72)	R,R-cyhex.	Me	H	R-α-MeBn	1 hr	82%	8% (R)
(75)	R,R-cyhex.	Me	H	S-α-MeBn	<10 min	84%	46% (R)
(76)	R,R-cyhex.	Me	H	benzyl	30 min	88%	19% (R)
(77)	racemic cyhex.	Me	benzyl	R-α-MeBn	>5 hrs	80%	racemic
(81)	R,R-cyhex.	H	Me	Me	90 min	90%	10% (R)
(82)	R,R-cyhex.	Me	Me	Me	2 hrs	88%	3% (R)
(83)	R,R-cyhex.	Me	--pyrrolidyl--		30 min	89%	2% (R)
(84)	S,S-diphenyl	H	H	R-α-MeBn	<10 min	87%	39% (S)
(85)	S,S-diphenyl	Me	H	R-α-MeBn	45 min	81%	23% (S)

* 0.6 equivalents of BMS added to a 1M THF solution of ketone and 10 mol% catalyst at rt.
** 5 mol% of catalyst was used.
*** See Figure 17.

The greatest reduction accelerations appear to be achieved with a primary exocyclic amide nitrogen (R^3=H). In examples in which R^3 and R^4 are alkyl both the reduction selectivity and rate of catalysis are significantly reduced, presumably due to steric effects. In the R, R-cyclohexyl series (R^1= cyclohexyl) greater selectivity is achieved when R^2 is methyl and R^4 is S-α methylbenzyl in which case the directing effect of all chiral centres is matched. The same trend is observed when R^2 is hydrogen. In the corresponding *trans*-diphenyl system (R^1=phenyl) reducing the size of the R^2 substituent from methyl to hydrogen improves selectivity, though the enantioselectivity is lower than that achieved with the cyclohexyl system. In both cases the absolute configuration of the product agrees with the proposed mode of ketone approach to phosphorus (Figure 18), though the actual transition states may be more complex than this simple model since the configuration of the R^4 substituent has a significant effect. Increasing the size of R^2 has a detrimental effect on both the rate of catalysis and selectivity, again presumably due to steric effects.

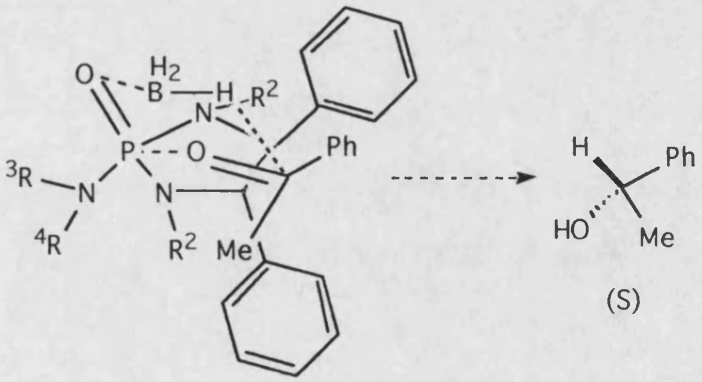
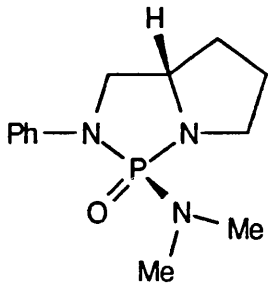


Figure 18
Possible transition state for
triamide catalysed reduction

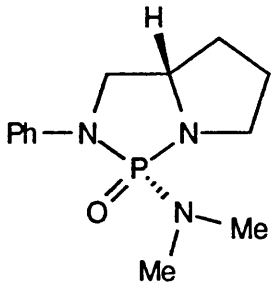
Section 2.5.2: Triamides Derived from Non-*C*2 Symmetric Diamines.

Though the C_2 symmetric diamide component of the catalysts appeared to have a moderate directing effect, the selectivity obtained with these systems was

modest. We next turned our attention to non-C_2 symmetric triamide structures such as (88) and (89).[75]



(88)

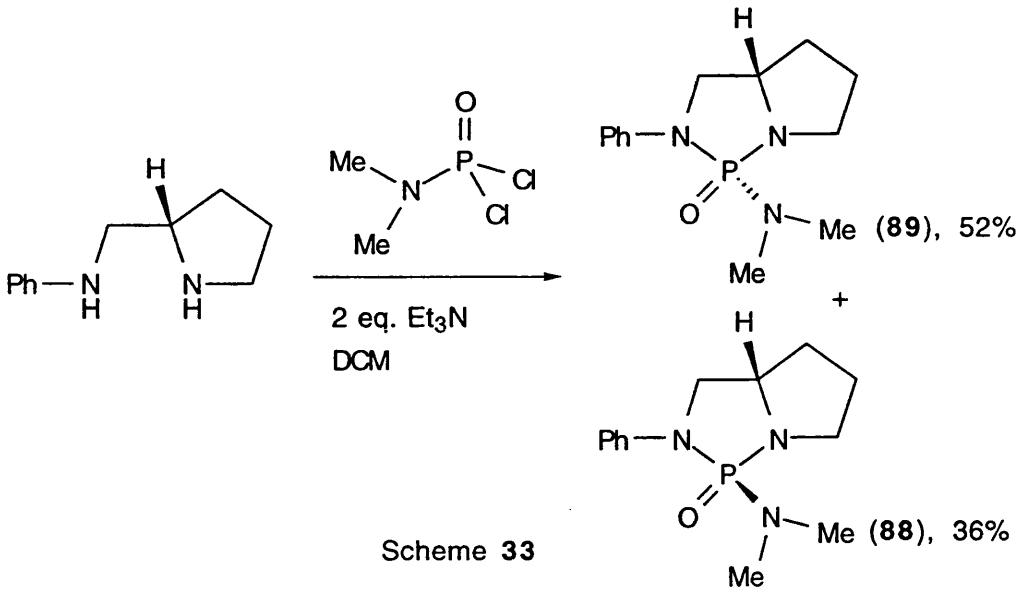


(89)

These compounds contain a rigid bicyclic ring system, the structure of which is similar to the corresponding oxazaborolidine systems.[20] This, we believed, would direct ketone approach to the convex face of the molecule; the phenyl group of the catalyst would then exert a steric influence on preferred orientation of ketone approach. Compounds of this type had been reported by Fiaud[75a] and the stereochemistry at phosphorus assigned by ^1H and ^{31}P NMR studies.

We prepared (88) and (89) in 88% yield as a 1.4:1 mixture of diastereoisomers (S, Rp (89) major) by reaction of commercially available S-2-(anilinomethyl)pyrrolidine with N, N-dimethylphosphoramido dichloridate (2 equivalents of triethylamine, DCM) as shown in Scheme 33.

Both diastereoisomers were easily separated by column chromatography and crystallisation. The results obtained using these compounds as catalysts for acetophenone reduction are shown in Table 13.



Scheme **33**

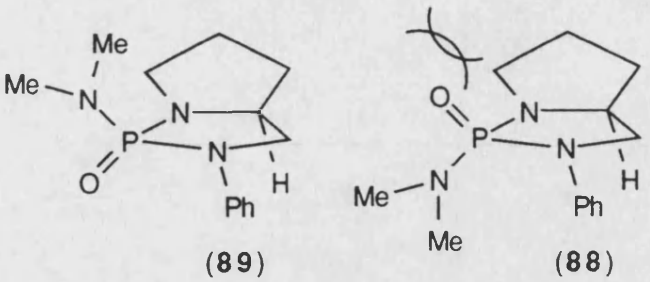
Catalyst*	Config.**	Time (>98% reduction	Yield (isolated)	e.e. (config.)
(**88**)	SSP	> 5 hrs	84%	racemic
(**89**)	SRP	2.5 hrs	82%	5% (R)

* 0.6 equivalents of BMS added to a 1M THF solution of ketone and 10 mol% catalyst in THF at rt.

** configuration assigned by comparison with literature data.[75a]

Table 13 Reduction of Acetophenone Catalysed by Triamides (**88**) and (**89**).

Both diastereoisomers appeared to give disappointingly low selectivity, again presumably due to steric crowding around the phosphorus atom. The S, RP diastereoisomer (**89**), in which the P=O bond has an *exo* configuration, appeared to be a more active catalyst than (**88**) due, we believed, to the greater accessibility of the P=O bond in this molecule for borane complexation. The corresponding S, SP diastereoisomer (**88**) contains an extremely hindered P=O bond (Figure 19).



(89) (88) Figure 19

At this stage we had achieved some success using the combined donor protocol and began to suspect that the problems with the catalytic system, namely poor transfer of 'chiral information', lay with ketone binding. We therefore began to examine ways in which this might be improved.

Section 2.6: The Problem of Ketone Binding.

A major problem with catalyst efficiency, we believed, was the poor Lewis acidity of the phosphorus atom once borane co-ordination had occurred (Figure 20).

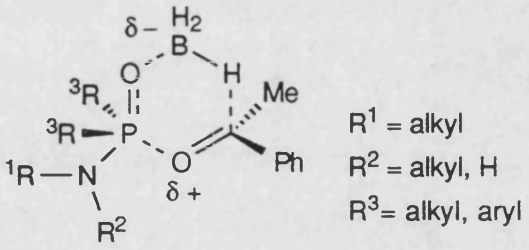


Figure 20

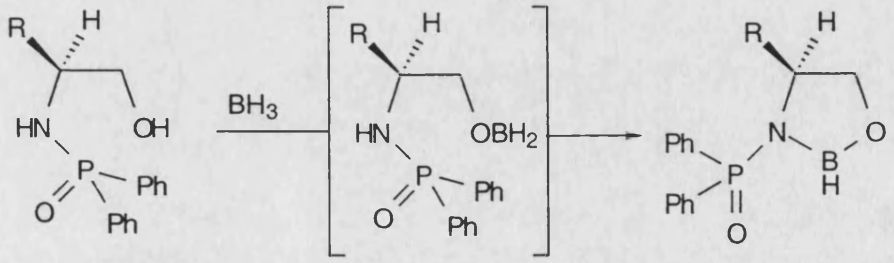
A semi-empirical molecular modelling study of the N-P=O catalysed reduction using AM1 with MOPAC94[77] confirmed that co-ordination of ketone to phosphorus was very weak and occurred at the latter stages of hydride transfer. In contrast in the corresponding oxazaborolidine mediated process the interaction of the carbonyl group lone pairs with the boron atom is considerably stronger.[25,78] These results are also reflected by the high reactivity rates observed using electron rich phosphinamides which demonstrates that donation is the dominant effect.

This interaction could possibly be made more favourable by adding electron withdrawing substituents to phosphorus, however we have demonstrated that electron withdrawing groups have a detrimental effect on selectivity since they also remove electron density from the P=O bond thus reducing the ability of the catalyst to 'activate' the borane reagent for hydride transfer. This results in loss of control in the transition state due to lack of rigidity.

An alternative strategy was to combine the excellent borane activating properties of the phosphinamide with a good electron density acceptor such as a boron derivative either as a single molecular entity, or as a bi-molecular co-operative system.

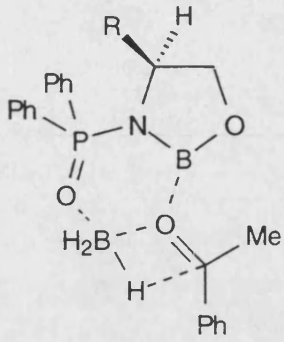
2.6.1 Amino Alcohol Derived Phosphinamides.

The diphenylphosphinyl group has been used as an effective protecting group in amino acid and peptide chemistry.[31] Similarly, Sweeney has prepared N-phosphinyl derivatives of a number of amino alcohols.[79] We believed that addition of borane to an N-phosphinylated amino alcohol would generate an alkoxy borane species such as (**90**), which could further react with the acidic N-H of the phosphinylated product in an intramolecular sense to give an oxazaborolidine such as (**91**) (Scheme 34).[80] The oxazaborolidine boron atom could then act as a Lewis acidic site for ketone co-ordination whilst the P=O bond could activate borane (Figure 21).



R= alkyl

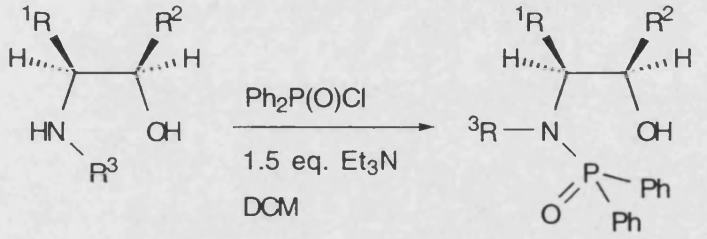
Scheme (**34**) (**90**) (**91**)



R= alkyl

Figure (**21**)

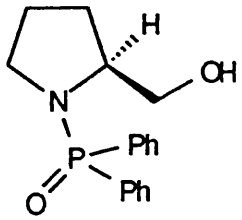
To explore this idea we prepared phosphinamides (**92**)-(**94**) from the corresponding amino alcohols (S-valinol, 1R, 2S-(-)-norephedrine and 1R, 2S-ephedrine respectively) by reaction with diphenylphosphinic chloride in DCM (1.5 equivalents of triethylamine) as shown in Scheme 35.



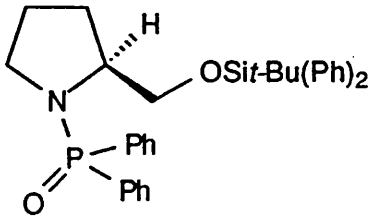
(**92**) R^1=*i*-pr, R^2 =R^3=H, 75%
(**93**) R^1=Me, R^2=Ph, R^3=H, 91%
(**94**) R^1=R^3= Me, R^2=Ph, 30%

Scheme **35**

In all cases the reaction proceeded with regioselective N-phosphinylation (presumably giving the thermodynamic product) with no O-phosphinoylation observed, though the lack of reactivity of the secondary nitrogen atom in the case of ephedrine resulted in a lower yield of (**94**), presumably due to competitive O-phosphinoylation and subsequent destructive side reactions tacking place. The corresponding S-proline derived compound (**95**) was prepared in 81% yield *via* the same route. The silyl protected analogue of this compound (**96**) was also prepared from (**95**) in 78% yield (*t*-BDPS-Cl, DMF, imidazole) for comparison of catalytic activity with its precursor. The results obtained using these derivatives as catalysts for acetophenone reduction are summarised in Table 14.



(95)



(96)

Catalyst*	Mol% catalyst	Time (>98% reduction)	yield (isolated)	e.e. (config.)
(92)	2	> 3 hrs	54%	10% (R)
(95)	2	2-3 hrs	72%	12% (R)
(93)	10	2 hrs	80%	10% (S)
(93)	2**	2-3 hrs	75%	8% (S)
(93)	100**	2 hrs	81%	11% (S)
(94)	2	2-3 hrs	71%	5% (S)
(96)	2	4 hrs	80%	7% (R)

* 0.6 equivalents of BMS added to a 1M solution of ketone and catalyst in THF at rt.

** A THF solution of catalyst was precomplexed with 1.1 equivalents of BMS for 8 hours at rt, then ketone was added followed by a further 0.6 equivalents of BMS.

Table 14 Reduction of Acetophenone Catalysed by Phosphinylated Amino alcohol / borane complexes.

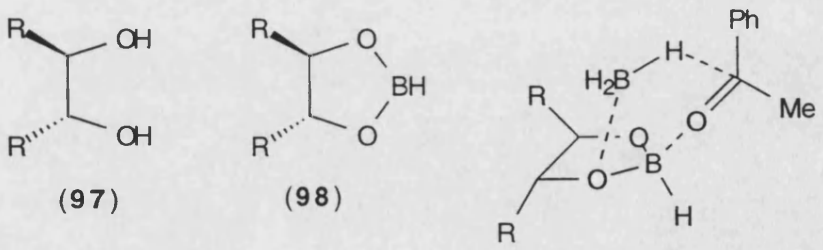
These compounds appeared to give lower selectivity and require longer reaction times than the simple phosphinamide systems previously examined. There appeared to be very little difference between the secondary (compounds (**95**) and (**94**)) and primary (compounds (**92**) and (**93**)) amide derivatives suggesting that oxazaborolidine formation may not have occurred under the reaction conditions employed. Both the ephedrine (**94**) and norephedrine (**93**) systems gave virtually identical results suggesting that the active catalyst in both cases was an acyclic alkoxyborane complex. Increasing the length of borane/ phosphinamide pre-

complexation time did not appear to increase selectivity or rate of reduction with the norephedrine derived phosphinamide (**93**).[81] Use of a stoichiometric quantity of this compound resulted in a negligible improvement in catalyst performance.

The silyl protected derivative (**96**) appeared to give slightly lower selectivity than the parent hydroxy compound and required a longer reaction time, though again the difference in catalyst performance appeared negligible. These results suggested that the presence of the hydroxy group was not beneficial to catalysis, though we still believed that an alkoxyborane species would improve ketone binding in the phosphinamide system. We therefore turned our attention to the use of boronate esters derived from simple chiral diols.

2.6.2: Chiral Diols / Phosphinamide Donors.

In view of the disappointing results obtained with the amino alcohol derived systems we turned our attention to the use of diols. Chiral diols such as (**97**) are known to form boronate complexes (**98**) upon reaction with borane. Although these complexes contain a third hydride they do not act as reducing agents since transfer of the third hydride is extremely slow. However, upon addition of further borane they have the potential to catalyse reduction by binding to ketone and borane as depicted in Figure 22.[84]

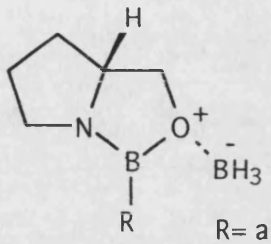


R= alkyl, aryl

Figure **22**

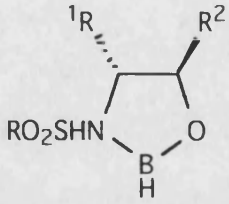
There a number of reports in the literature of borane-O adducts.[81,83] *Ab-initio* molecular orbital calculations on the proposed oxazaborolidine catalysed

reduction mechanism have demonstrated that the reaction pathway *via* a borane-O adduct (**99**) is much less plausible than the accepted N-adduct previously described. However, it is well known that borane forms complexes with ethers such as THF.[121,82]



(99)

Katsuki has recently reported that chiral N-sulfonyloxazaborolidines such as (**100**) are capable of catalysing the enantioselective reduction of ketones giving an enantiomeric excess of 47% in the case of acetophenone.[81] An oxygen-borane adduct was postulated as the likely intermediate in the reaction (Figure 23).



(100), R=R^1=Me, R^2=Ph

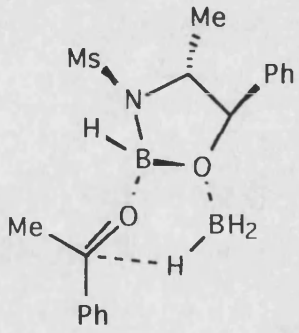


Figure 23

Garcia[83] has reported that boronate complexes such as (**98**, R= Ph, -CO_2Me), formed *in situ* from the corresponding diol, do not show catalytic activity, though it seemed likely to us that ketone binding should occur with these complexes and that it was their weak interaction with borane which limited their performance as efficient catalysts ; the weak donation to borane resulting in slow hydride transfer. We believed that the ketone binding properties of boronate

complexes such as (**98**) coupled with the donor characteristics of the phosphinamides should enhance the effect of both.

Our initial investigations involved the use of the chiral diols (**97**, R=Me) and (**97**, R=Ph). The borane complexes of these compounds (**98**) were prepared *in situ* by complexation of the R, R-diol with 1.1 equivalents of BMS in THF at rt for 20 minutes.[83] We first examined the use of these complexes as catalysts for acetophenone reduction. The results are summarised in Table 15.

Catalyst*	Mol% catalyst	Time (>98% reduction)	Yield (isolated)	e.e. (config)
none	-	> 12 hrs	75%	-
(**98** R=Me)	10	>12 hrs	< 20%**	21% (S)
(**98**, R=Me)	100	3-4 hrs	72%	41% (S)
(**98**, R=Ph)	100	3 hrs	90%	42% (S)
(**98**, R=Ph)	100***	2-3 hrs	89%	15% (S)

* 0.6 equivalents of BMS added to a 1M THF solution of ketone and boronate complex (**98**) (formed *in situ* by complexation of the R, R-diol with 1.1 equivalents of BMS in THF at rt for 20 minutes) at rt.
** Mainly unreacted ketone after 12 hours.
*** Diol/ borane complexed for 16 hours at rt prior to ketone addition.

Table 15 Reduction of Acetophenone Catalysed by Boranate (**98**).

The use of 10 mol% of (**98**, R=Me) in the reaction gave modest selectivity, although a very low yield of alcohol; the reaction mixture consisting mainly of unreacted ketone after stirring overnight. Repeating the reaction using an equimolar quantity of the same complex gave a reduction product of 41% e.e. with complete consumption of starting material. This suggested that at lower concentrations the complex had little or no catalytic activity (in terms of catalyst turnover) whilst at the higher concentration, presumably at which all of the ketone was complexed, poor catalyst recycling would not limit selectivity.

Increasing the size of the R- substituent in (**97**) from methyl to phenyl appeared to have no effect on selectivity, however complexation of the diol with borane for extended lengths of time in forming (**98**, R=Ph) appeared to have a detrimental effect on selectivity, presumably due to partial decomposition of the boronate complex.

The S- configuration of the resulting alcohol appeared to agree with that predicted by the model illustrated in Figure 22. Assuming borane is attached *trans* to the adjacent R- group in (**98**) and the carbonyl group attached *via* the lone pair *trans* to the phenyl with the methyl group orientated away from the bulky catalyst, the predicted selectivity matches that observed.[111]

Having demonstrated the ability of the ketone to co-ordinate to the boronate complex in these systems we next examined the effect of a combination of phosphinamide (**29**) with the boronate complex (**98**) in the reduction reaction. The results are summarised in Table 16.

Boronate complex*	Mol% boronate complex**	Mol% (**29**)	Time (>98% reduction)	Yield (isolated)	e.e. (config.)
none	-	10	< 1 hr	82%	26% (S)
(**98**,R=Me)	10	none	>12 hrs	< 20%	21% (S)
(**98**,R=Me)	10	10	2 hrs	89%	47% (S)
(**98**,R=Me)	100	10	90 min	88%	56% (S)
(**98**,R=Me)	100	100	< 1 hr	74%	35% (S)
(**98**,R=Ph)	10	10	4 hrs	87%	52% (S)
(**98**,R=Ph)	100	10	2-3 hrs	91%	41% (S)

* Formed *in situ* by complexation of the diol with 1.1 equivalents of BMS in THF at rt for 20 minutes.

** 0.6 equivalents of BMS added to a 1M THF solution of ketone, boronate complex (**98**) (formed as described above) and phosphinamide (**29**) at rt.

Table 16 Reduction of Acetophenone Catalysed by Phosphinamide (**29**) in Combination with Boronate (**98**).

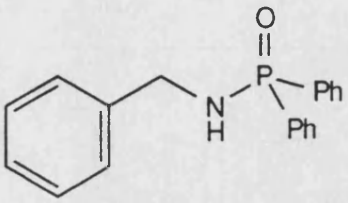
Gratifyingly, the combination of phosphinamide (**29**) together with (**98**) gave higher levels of asymmetric induction than when used individually. The use of 1 equivalent of boronate complex together with a catalytic quantity of phosphinamide appeared to increase selectivity, though a stoichiometric quantity of both components gave a lower result, presumably due to the dominating effect of the phosphinamide. The use of a catalytic quantity of boronate (**98**, R=Ph) together with phosphinamide (**29**) appeared to give better selectivity than in the corresponding methyl system (**98**, R=Me) though, for reasons that are not clear, increasing the concentration of the complex appeared to have a detrimental effect on selectivity.

These results suggested that the two materials were working together in a process in which their enantioselectivities were matched, this presumably being achieved by donation of electron density from the P=O bond in (**29**) to the borane molecule appended to the oxygen atom in Figure 22, which underlines the productive collaboration of a good donor (**29**) and acceptor (**98**).

In order to eliminate the possibility that the phosphinamide was facilitating reduction by transfer of the third hydride from boronate (**98**) rather than borane,[87] a THF solution of 10 mol% phosphinamide (**29**), 1 equivalent of boronate complex (**98**, R=Me) and ketone was stirred for 18 hrs at room temperature after which time no alcohol was observed. Addition of a further 0.6 equivalents of BMS resulted in >98% reduction of acetophenone in 90 minutes giving an alcohol of 54% e.e. (S major, 83% yield).

In order to assess the importance of the α-methylbenzyl chiral centre in directing the reduction and substantiate the combined donor/ acceptor effect we conducted an experiment using 10 mol% of achiral phosphinamide (**101**), prepared in 91% yield by reaction of benzyamine with diphenylphosphinic chloride (2 equivalents of triethylamine, DCM) and 10 mol% (**98**, R=Me). This combination gave an alcohol product of 14% e.e. (S major, 86% yield) in 3 hours at room temperature, which suggested that the phosphinamide was intimately involved in

controlling not only rate of catalysis but also reduction selectivity.



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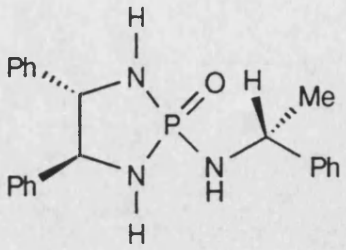
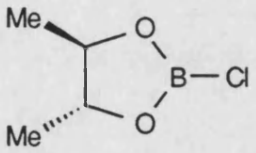


(84)

Repeating the experiment using 10 mol% of triamide (**84**), which we knew gave good S- reduction selectivity (Section 2.5) resulted in a considerable erosion of selectivity in the presence of the boronate complex (23% e.e. compared with 40% without the boronate present), with a reaction time in excess of 5 hours being required for >98% reduction of the ketone. The reasons for this are again not immediately apparent.

We next wished to examine the effect of varying the boron substituent in (**98**) on the performance of the boronate complex in the reduction reaction and therefore turned our attention to boronates (**102**) and (**103**).



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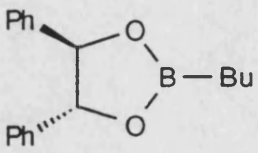


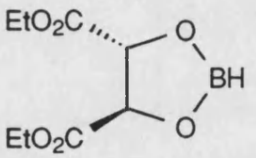
(103)

We reasoned that increasing the Lewis acidity of the boron atom in (**98**) by introduction of a chlorine atom should allow the carbonyl group to complex more strongly.[14a] To this end we prepared boronate (**102**) *in situ* by reaction of diol (**97**, R=Me) with 1.1 equivalents of monochloroborane in THF at room temperature. The use of 10 mol% of this complex together with 10 mol% of phosphinamide (**29**) gave a reduction product of 14% e.e. (S, major, 61% yield) in 3 hours at room

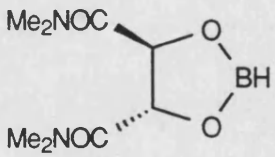
temperature, however partial decomposition of the phosphinamide under the reaction conditions was also observed using this material, presumably due to the increased Lewis acidity of the diol complex.[85,79a]

Boronate ester (**103**) was prepared in 95% isolated yield by reaction of the diol (**97**, R=Ph) with butyl boronic acid in pentane at room temperature.[83,86] 10 mol% of this compound together with 10 mol% of phosphinamide (**29**) gave a reduction product of 25% e.e. (S major, 88% yield) in 4 hours at room temperature (c.f. boronate (**98**, R=Ph), 52% e.e., 4 hours). It thus appeared that increasing the size of the boron substituent had a detrimental effect on selectivity, again presumably due to steric effects.

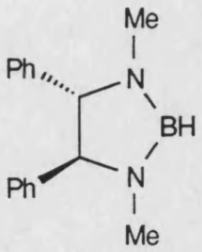
To complete our examination of the scope of this process we investigated the tartrate- derived boronates (**104**) and (**105**) (prepared *in situ* from the corresponding diol and BMS as described above) and the diamine derivative (**106**) (prepared *in situ* by reaction of the diamine with BMS in THF at room temperature) in combination with phosphinamide (**29**). The results obtained are summarised in Table 17.



(**104**)



(**105**)



(**106**)

Boronate*	Time (>98% reduction)	Yield (isolated)	E.e. (config.)
(**104**)	> 5 hrs	88%	35% (S)
(**105**)	> 5 hrs	79%	10% (S)
(**106**)	2-3 hrs	81%	17% (S)

* 0.6 equivalents of BMS added to a 1M THF solution of ketone, 10 mol% of boronate (formed *in situ* by complexation of the diol with 1.1 equivalents of BMS in THF at rt for 20 minutes) and 10 mol% of phosphinamide (**29**) at rt.

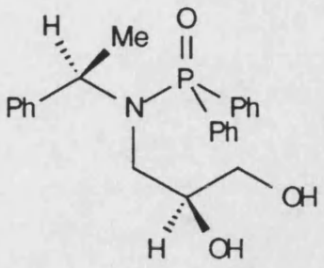
Table 17 Reduction of Acetophenone Catalysed by Phosphinamide (**29**) in Combination with (**104**)-(**106**).

In all cases reduction appeared slow and the selectivities were lower than the corresponding alkyl boronates (**98**). Diethyl tartrate- derived boronate complex (**104**) together with phosphinamide (**29**) gave overall S- reduction selectivity though in this case the configuration of the boronate may not have been 'matched' with that of the phosphinamide. The corresponding S, S- diamide (**105**), however, gave the same major reduction product but in lower enantiomeric excess. Decomposition of boronate complex (**104**) occurred during the reaction possibly as a result of reduction of the ester functionality.[121] Diamine complex (**106**) did not appear as effective as the corresponding alkyl boronate complex (**98**, R=Ph) in this process. This was surprising since it would be expected to behave more like an oxazaborolidine than (**98**).[122] The formation of an acyclic amine-borane complex on adding BMS to the diamine rather than (**106**) could account for this lack of reactivity.

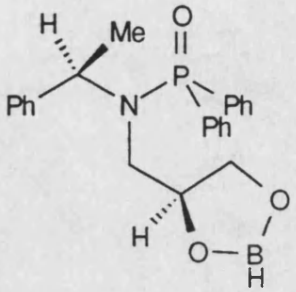
2.6.3: Phosphinamide / Diol as a Single Molecular Entity.

Having established that the presence of a boronate complex considerably improved the selectivity of the phosphinamide catalysed reduction, we planned to

capitalise on these observations by combining the N-P=O structural unit and the diol motif into a single molecular entity.



(107)



(108)

Phosphinamide diol (**107**), we believed, upon reaction with borane should generate the active catalytic species, boronate (**108**), *in situ*. The ketone could then co-ordinate with the electron accepting boron atom *via* an interaction with one of the oxygen lone pairs as shown (Figure 24). This would result in removal of electron density from the carbonyl group and consequently increase its reactivity (in much the same way as the oxazaborolidine system). Complexation of the ketone could then occur on either face of the borocyclic ring to give **X** or **Y** respectively (Figure 24). Borane (stoichiometric reductant) is then free to co-ordinate to either one of the ring oxygen atoms lone pairs; complex **X** giving **A** or **B** whilst **Y** would give **C** or **D**. Since this interaction is known to be weak, the borane is not significantly activated in terms of reactivity. In complex **A**, however, the phosphinamide can adopt a suitable conformation to donate electron density and promote hydride transfer to the co-ordinated ketone. Since the borocyclic ring of the catalyst is also sterically demanding, co-ordination of the ketone *via* its lone pairs should occur with the methyl group orientated away from the bulky ring system; hydride should then be delivered to the *re* face giving the S- enantiomer of product.

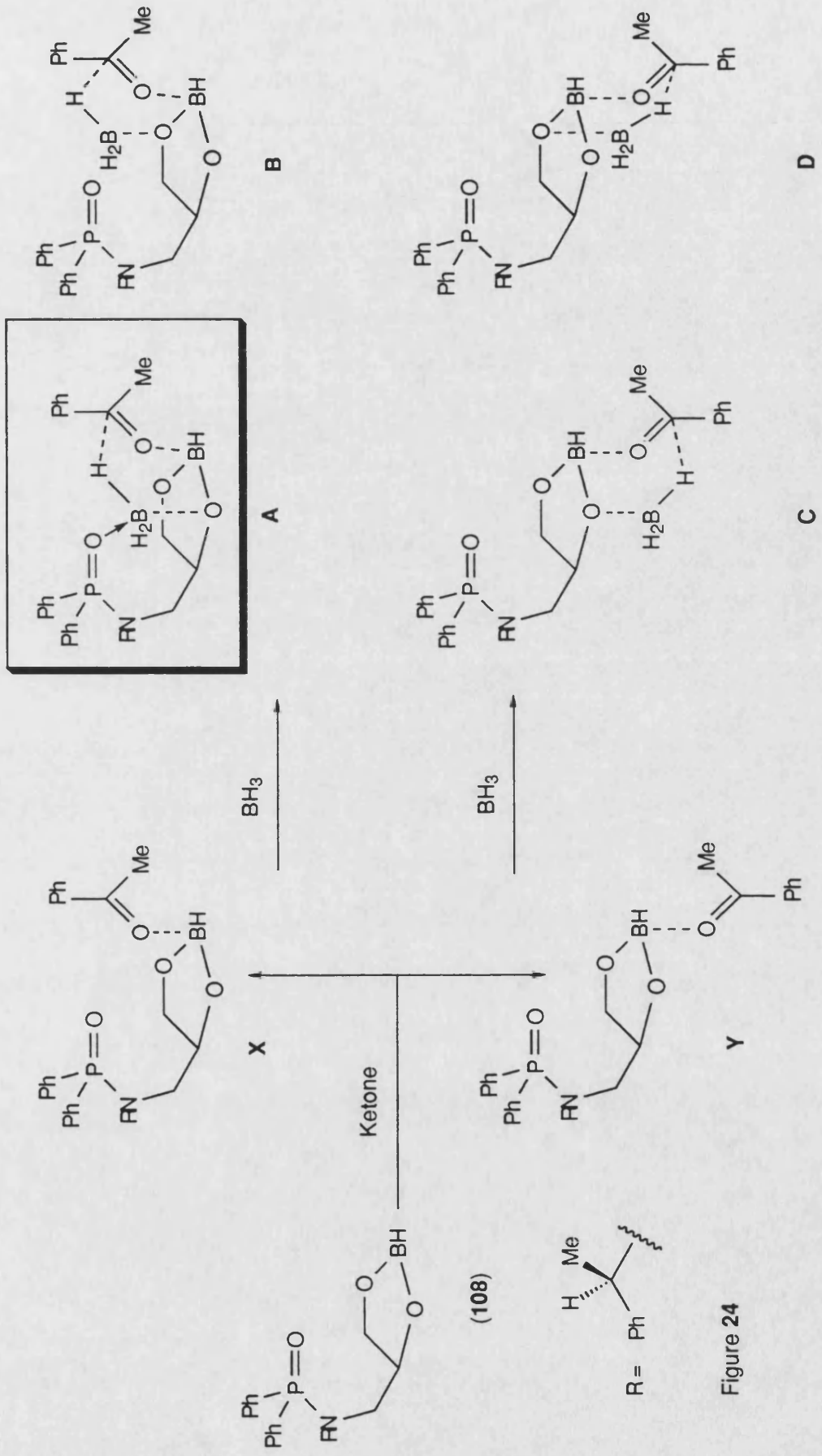
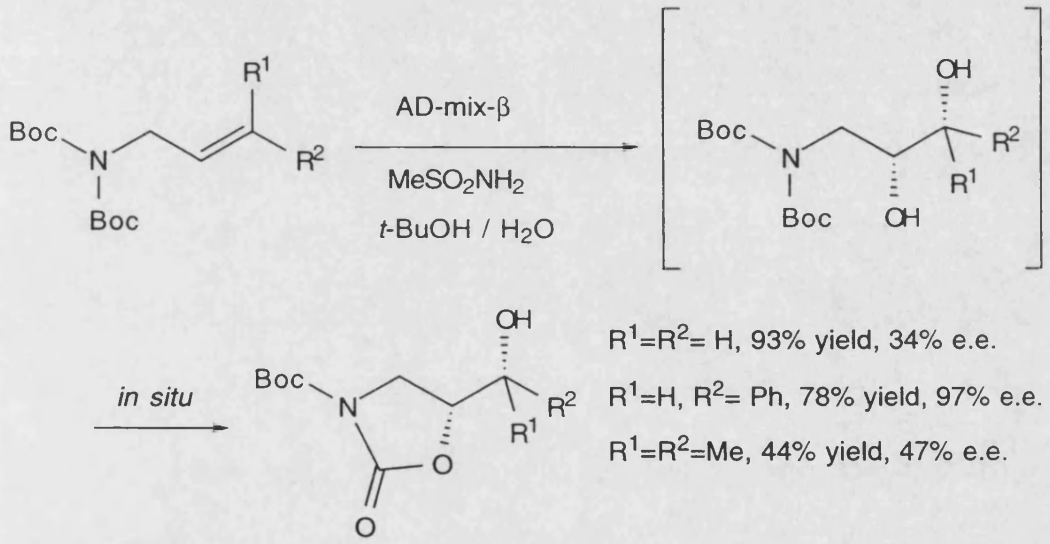


Figure 24

2.6.3.1 Preparation of Phosphinamide Diols by Asymmetric Dihydroxylation.

In order to explore this idea we required a route to diastereomerically pure phosphinamide diol (**107**). One very effective synthetic route to chiral diols is the Sharpless asymmetric dihydroxylation of the appropriate olefin.[88] This methodology has been successfully applied to a number of di-BOC protected allylic amines, with good selectivity reported for di- and tri- substituted double bonds (Scheme 36). Though no examples of dihydroxylation of diphenylphosphinyl protected allylic amines had been reported, we believed this represented a very effective method for assembling these compounds in homochiral form.

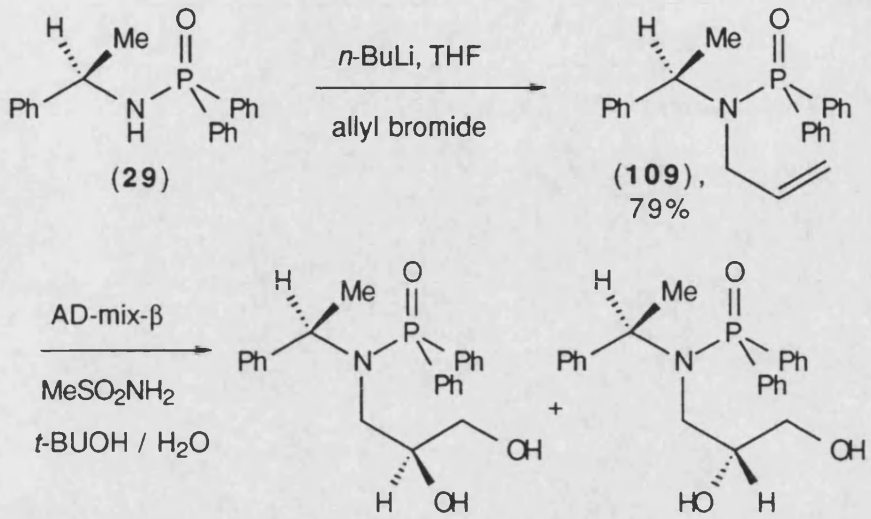


Scheme **36**

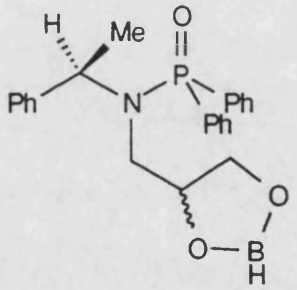
To this end we prepared alkene (**109**) in 79% yield by alkylation of (**29**) (1.2 equivalents of *n*-BuLi, THF, allyl bromide) (Scheme 37).

Dihydroxylation of (**109**) under standard Sharpless conditions using AD-mix-β[88,89] (1mmol alkene, 1.4g AD-mix, *t*-butanol/water) gave a 91% yield of a 1.7:1 mixture of diastereomeric diols (ca. 30% d.e., as assessed by ^{1}H and ^{31}P NMR) (Scheme 37), with the R, R-diastereoisomer being in excess. The diol configuration was determined by comparison of NMR data with a pure sample of the corresponding R, S-diastereoisomer prepared later (see below). The poor

dihydroxylation selectivity obtained with alkene (**109**) was consistent with that reported by Sharpless for di-BOC protected terminal alkenes (Scheme 36).



Scheme **37**



(**110**) RR:RS 1.7:1

All attempts to separate the mixture by chromatography and crystallisation proved unsuccessful, however use of 10 mol% of the boronate complex (**110**) (formed *in situ* by reaction of a THF solution of the diol mixture with BMS at rt) in the reduction of acetophenone gave a reduction product of 16% e.e. (S major, 84% yield), >98% reduction occurring in 3 hours at room temperature. 'Correction' of this value for catalyst purity and assuming that no synergic effects were in operation, this result suggested that a diastereomerically pure sample should give an enantiomeric excess in excess of 80%.

Encouraged by this preliminary result, we next wished to examine the effect of changing the configuration of the hydroxy centre at C-2 in order to determine if the directing effect of the amide side chain was significant. Remarkably, attempted dihydroxylation of alkene (**109**) using AD-mix-α, which should again have given a diastereomeric mixture of diols though in this case enriched in the R, S-diastereoisomer as a result of preferential oxidation of the opposite face of the alkene, resulted in the formation of the same mixture of diastereoisomers in 72% yield and in an identical ratio.

Intrigued by this result and the apparent overriding effect of the α-methylbenzyl chiral centre in determining face selectivity, we repeated the dihydroxylation of alkene (**109**) in the absence of the phthalazine ligand (1 equivalent of alkene, 3 equivalents of $K_3Fe(CN)_6$, 3 equivalents of K_2CO_3, 1 mol% $K_2OsO_2(OH)_4$, 1 equivalent of H_2NSO_2Me, *t*-Butanol/ water). This again appeared to give the same product mixture in 74% yield.

We believed this apparent directing effect to be due to intramolecular co-ordination of the P=O bond to osmium during the dihydroxylation, prior to rearrangement of the osmaoxetane intermediate and generation of the glycolate ester, preventing co-ordination of the phthalazine ligand and hence transfer of stereochemical information (Figure 25). The uncatalysed reaction appeared to proceed at a comparable rate (ca. 6 hrs at room temperature) to those under AD-mix control suggesting that a neighbouring group interaction may be in operation.

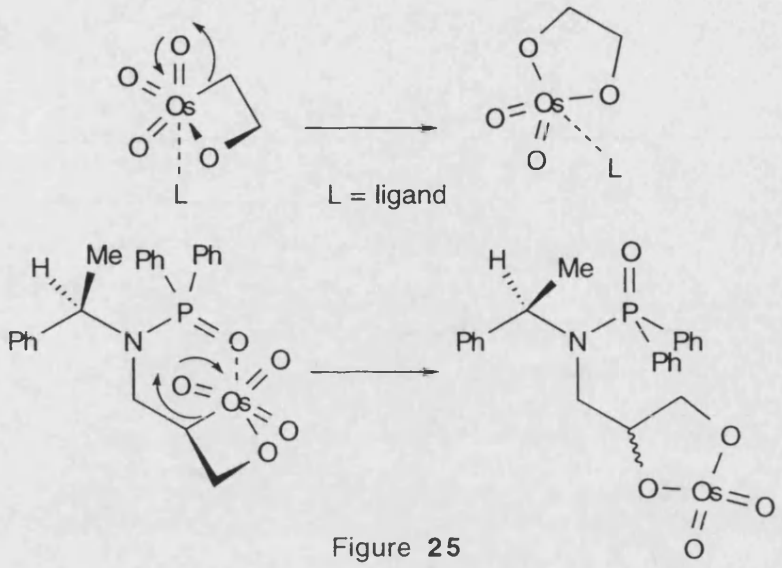
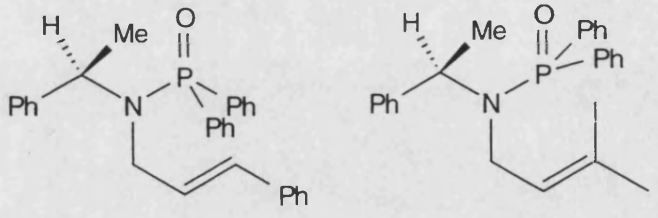


Figure 25

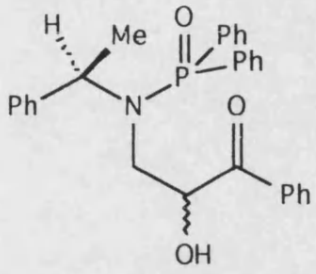
Despite all attempts to separate the diastereoisomers by physical methods and chemical derivatisation no pure samples could be obtained. We still felt, however, that the dihydroxylation reaction could be utilised for preparing structurally related phosphinamide diols and felt that this warranted further investigation. Substitution of the double bond in (**109**) could, we believed, improve oxidation selectivity. Also structural analogues of diol (**107**) might be easier to separate from a diastereomeric mixture. To this end we prepared alkenes (**111**) and (**112**) in 87 and 74% yields respectively from phosphinamide (**29**) under previously described conditions (1.2 equivalents of *n*-BuLi, THF, allylic halide).



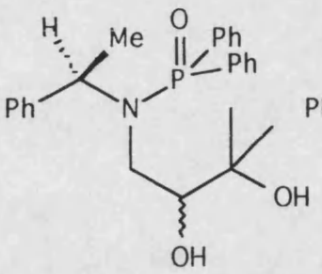
(**111**) (**112**)

Attempted dihydroxylation of (**111**) using AD-mix-β (1 equivalent alkene, 420 mg AD-mix, *t*-butanol/water) gave a 76% yield of the corresponding α-hydroxy ketones (**113**) as an inseparable 1.3:1 mixture of diastereoisomers, presumably as a

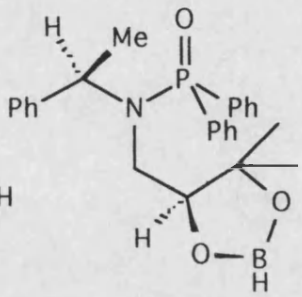
result of over- oxidation of the benzylic hydroxy group under the reaction conditions; a phenomenon usually only observed with strong oxidising agents such as alkaline permanganate.[109] This result seemed especially surprising in that dihydroxylation of conjugated alkenes such as stilbene under Sharpless AD-mix conditions results in a virtually quantitative formation of the diol with no over-oxidation observed.[45,110]



(113)



(114)



(115)

Treatment of a THF solution of the mixture with BMS gave a complex mixture of diastereomeric diols which could not be separated.

Dihydroxylation of alkene (**112**) using AD-mix-β (1equivalent alkene, 360 mg AD-mix, *t*-butanol/water) proceeded in 91% yield, again giving an inseparable mixture of diastereomeric diols (**114**) in a ratio of 1.6:1 (ca. 25% d.e.).

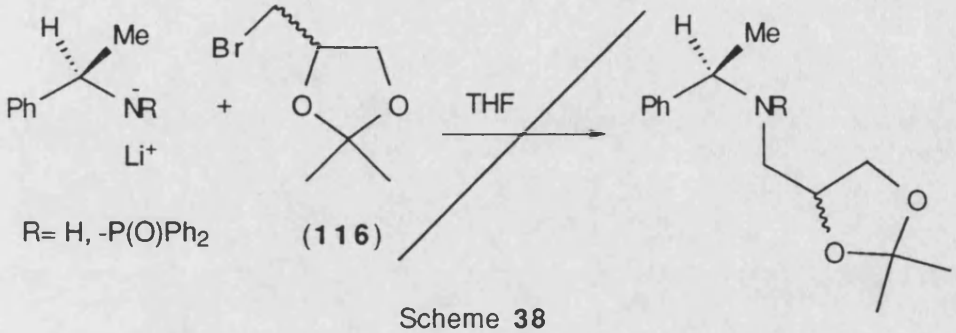
Use of 10 mol% of the boronate complex of this mixture (**115**) (prepared *in situ* by reaction of the diol mixture (**114**) with BMS at room temperature) gave a reduction product of 9% e.e. (S major, 84% yield), with >98% reduction occurring in 5 hours at room temperature. It seemed likley that the lower selectivity and longer reaction time required for reduction reflected the increase in steric crowding in boronate (**115**) relative to (**110**).

2.6.3.2 Preparation of Phosphinamide Diols from Chiral Glycidol.

At this stage the low selectivities and difficulty of diastereoisomer

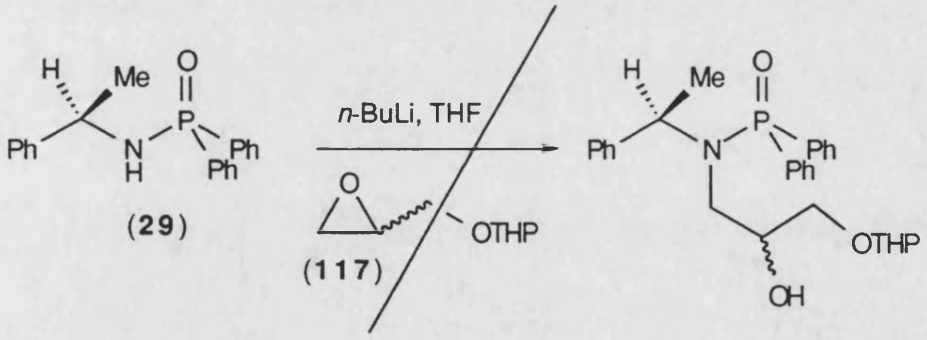
separation suggested that the asymmetric dihydroxylation reaction would not provide a means of preparing the requisite diastereomerically pure phosphinamide diols. We therefore turned our attention back to (**107**) and began to examine other routes to this compound.

Alkylation of both R-(+)-α methylbenzylamine and phosphinamide (**29**) using bromide (**116**)[90] (1.2 equivalents of *n*-BuLi, THF, bromide (**116**)) proved unsuccessful (Scheme 38), presumably due to the low reactivity of α-heterosubstituted halides to nucleophilic attack.[91]



Scheme **38**

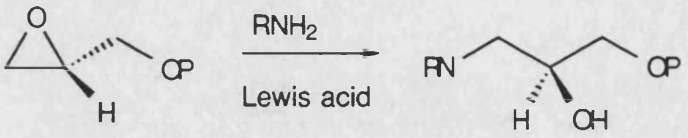
Similarly, attempted ring opening of THP- protected glycidol (**117**)[93] with deprotonated phosphinamide (**29**) proved unsuccessful (Scheme 39).



Scheme **39**

Lewis acid mediated ring opening of epoxides with amines has been used for the preparation of amino alcohols.[92] Similarly, glycidol derivatives have been ring opened at C-3 generating amino diols.[92b] Since homochiral glycidol[93] is readily

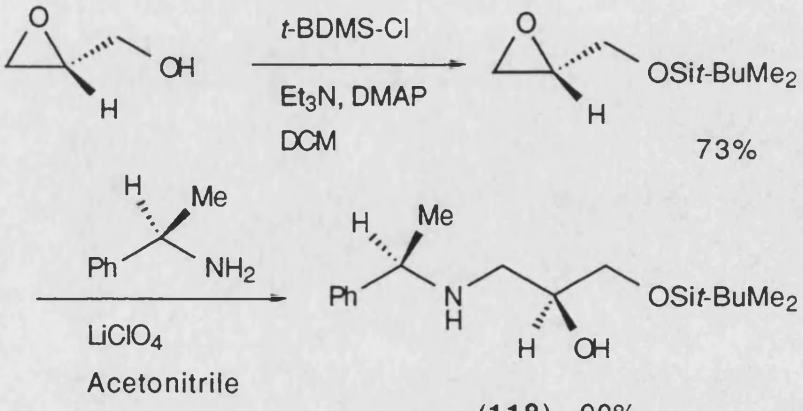
available we were particularly interested in this process since regioselective ring opening at C-3 would generate the required 1, 2-dihydroxy-3-amino motif required for the phosphinamide diol catalysts (Scheme 40).



P = protecting group
R = alkyl

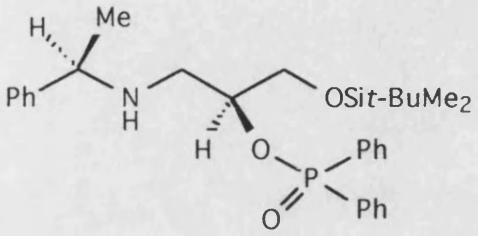
Scheme **40**

Reaction of R-(+)-α methylbenzylamine with R-glycidol using lithium perchlorate as catalyst[92c] (1 equivalent of amine and epoxide, 1 equivalent of lithium perchlorate, acetonitrile, rt) gave low yields of the required amino diol largely due to loss of material as a result of high water solubility. The polarity of the product also made purification difficult. Repeating the reaction with *t*-BDMS-protected glycidol[94] (prepared in 73% yield using 1.1 equivalents of *t*-BDMS-Cl, 1.2 equivalents of triethylamine and 0.05 equivalents of DMAP in DCM at rt.) gave the corresponding mono protected amino diol (**118**) in 90% yield as a single regioisomer (as assessed by ^{1}H and ^{13}C NMR) (Scheme 41). The corresponding *t*-BDPS protected epoxide gave a very low yield (<15%) of ring-opened product presumably due to the steric effect of the larger protecting group.



Scheme **41**

Remarkably, attempted phosphinylation of (**118**) using diphenylphosphinic chloride in DCM (2 equivalents of triethylamine) gave the O-diphenylphosphinoylated product (**119**) in 48% yield. This, we believed, may have been due to the greater thermodynamic stability of O-phosphinoylated secondary alcohols (in amino alcohols in which both the amine and alcohol are primary regioselective N-phosphinylation occurs in high yield[79], see Section 2.6.1). Another possibility is that phosphinoyl group migration from nitrogen to oxygen may have taken place during the reaction (Figure 26) though this usually requires acid catalysis.[79b]



(119)

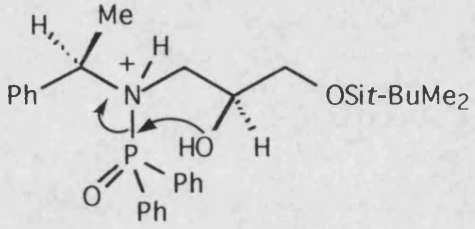
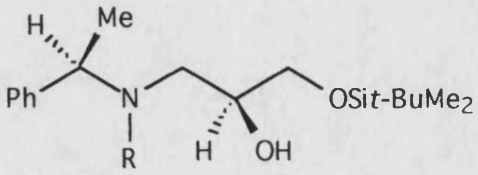


Figure 26

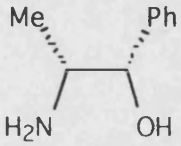
In order to prevent O-phosphinoylation we attempted to protect the hydroxy group as its *t*-BDMS- ether. Reaction of mono protected amino diol (**118**) with *t*-BDMS-Cl (1.2 equivalents of triethylamine, 0.05 equivalents of DMAP, DCM, rt) gave the corresponding N-silylated product (**120**) in 56% yield. Repeating the reaction using DMF/ imidazole (1 equivalent of *t*-BDMS-Cl, 2.2 equivalents of imidazole, DMF, rt) gave a 52% yield of the same product.



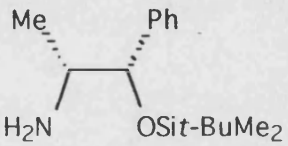
R = Si*t*-BuMe2

(120)

This result seemed at first surprising, though similar observations have been reported in the literature. For example Dunlap has found that treatment of 1S, 2R-norephedrine (**121**) with *t*-BDMS-Cl in the presence of triethylamine afforded what appeared to be a mixture of protected amine and alcohol in variable ratios, however it was found that refluxing this mixture in benzene gave the corresponding silyl ether (**122**) exclusively.[95] Refluxing *bis*-silylamino alcohol (**120**) for 6 hours in toluene resulted in no silyl migration.



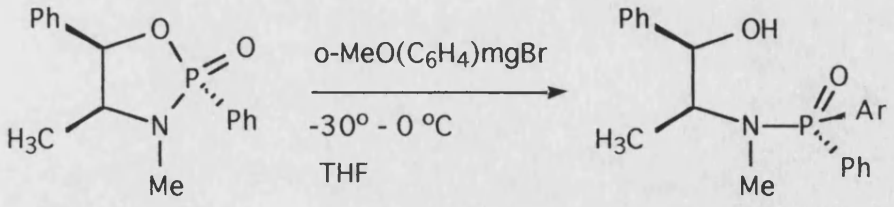
(121)



(122)

At this stage we had established an effective method for preparation of the diastereomerically pure 1, 2-dihydroxy-3-amino framework, but still required a reliable method for regioselective phosphinylation of the nitrogen atom.

Brown[96] had reported that reaction of oxazaphospholidine (**27**) with alkyl magnesium halides or organolithium reagents proceeded with regioselective cleavage of the primary P-O bond giving the corresponding protected amino alcohol (**123**) as a single diastereoisomer with overall retention of configuration at phosphorus (Scheme 42).[97]

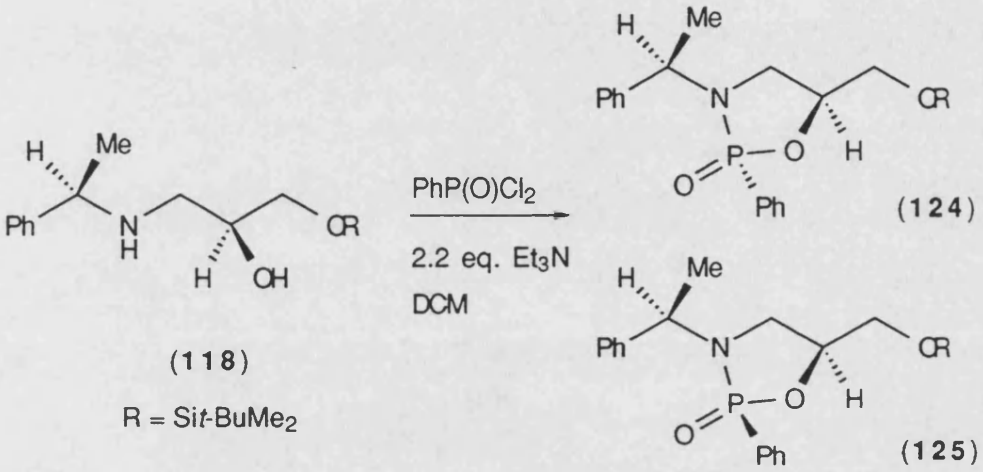


(27) (123), 70% (retention)

Scheme 42

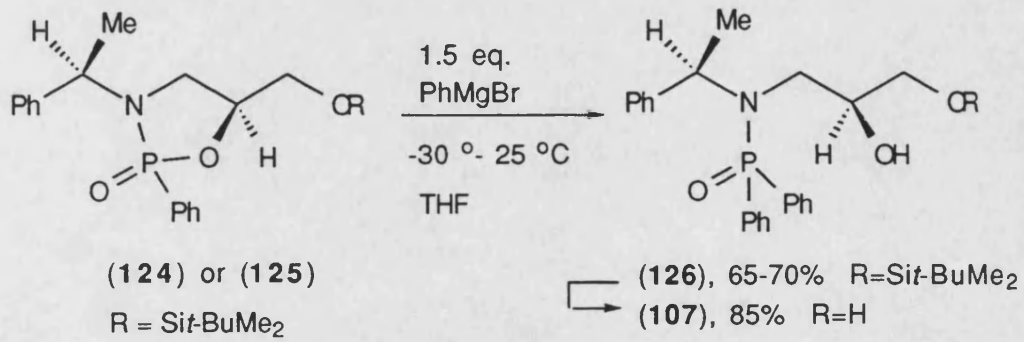
To examine the use of this strategy for the N-phosphinylation of (**118**) we

prepared epimeric oxazaphospholidines (**124**) and (**125**) in 45% yield and in a ratio of 1.4:1 by reaction of mono protected amino diol (**118**) with phenylphosphonic dichloride (2.2 equivalents of triethylamine, DCM, rt) (Scheme 43). The epimeric oxazaphospholidines (**124**) and (**125**) were readily separated by flash chromatography. The absolute configuration at phosphorus was inconsequential (since this chiral centre would be destroyed on ring opening) and was therefore not determined.



Scheme **43** 45%, 1.4:1

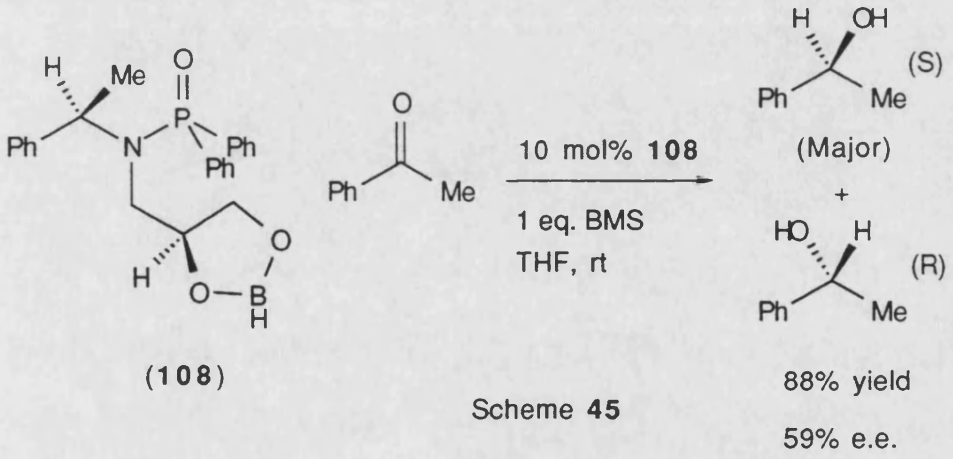
Treatment of a THF solution of either epimer with 1.5 equivalents of phenylmagnesium bromide[47] at -30 °C followed by warming to room temperature gave the N-phosphinylated amino alcohol (**126**) in 65-70% yield as a colourless oil (Scheme 44).



Scheme **44**

Cleavage of the silyl- group using 2 equivalents of TBAF (THF, 0 °C) gave the R, S-phosphinamide diol (**107**) in 85% yield. This compound was spectroscopically identical to one diastereoisomer in the mixture obtained by dihydroxylation of alkene (**109**). Comparison of ^{1}H and ^{31}P NMR data revealed that phosphinamide diol (**107**) was the minor component of the diastereomeric mixture obtained *via* the oxidation route. The pure R, S-diastereoisomer was then screened for catalytic activity.

In situ complexation of (**107**) with BMS in THF at room temperature for ca 2 hours (presumably generating boronate (**108**)) followed by addition of acetophenone and a further equivalent of BMS resulted in >98% reduction in 3 hours at room temperature. The resulting alcohol was obtained in a disappointing 9% e.e. (S major, 82% yield).

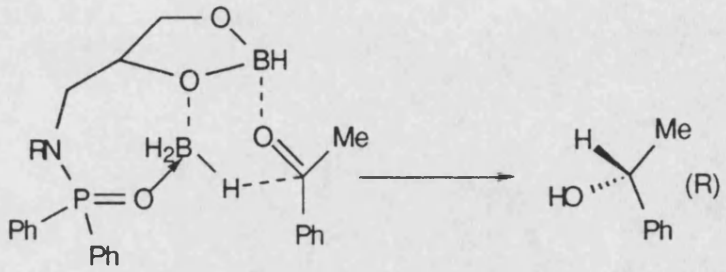


Scheme **45**

We were concerned that boronate (**108**) may be considerably more sensitive to reaction conditions than the phosphinamide catalysts alone,[28] and believed that the presence of impurities might have a more pernicious effect on catalyst performance. Phosphinamide diol (**107**) was further purified by double crystallisation from diethyl ether/ pentane and dried *via* azeotropic removal of water using chloroform. The ketone (initially dried by distillation from calcium hydride) was dissolved in THF and dried for 18 hours over activated 4Å molecular sieves prior to use.[28,118] The reduction was then repeated under rigorously anhydrous

conditions and gratifyingly the alcohol was obtained in 59% e.e. (S major, 88% yield) after 2 hours at room temperature (Scheme 45).

Again we believed that the α methylbenzyl chiral centre was contributing significantly to the selectivity observed since if the configuration of the chiral centre at C-2 were the only controlling element, the ADH reaction product (containing ca. 30% d.e. of the R, R-diastereoisomer) would have been predicted to give the opposite enantiomer of alcohol in the reduction (Figures 24 and 27).



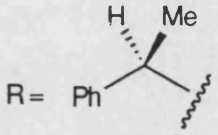
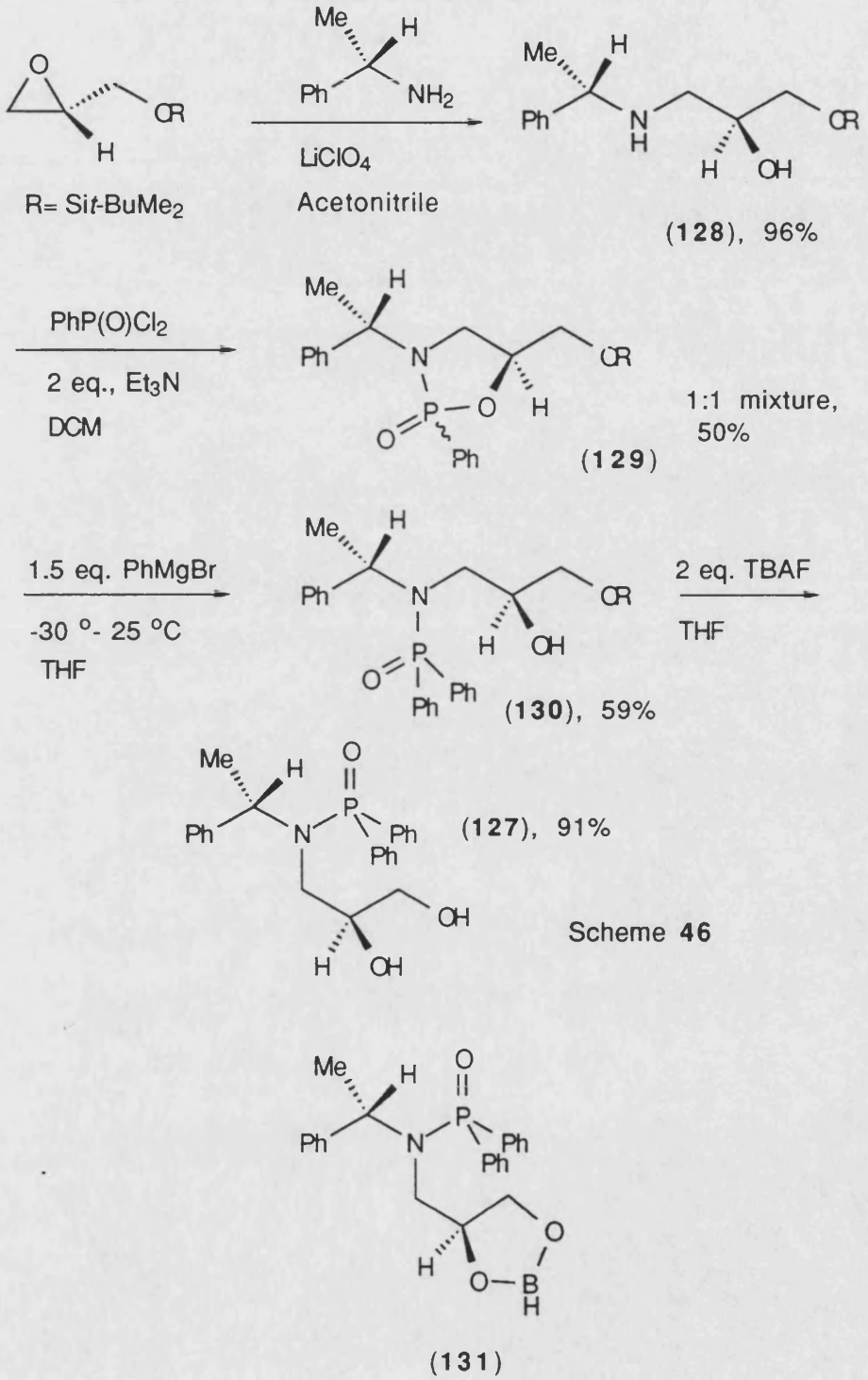


Figure 27

To examine these effects in more detail we prepared a pure sample of the S, S-phosphinamide diol (**127**), the enantiomer of the major component of the ADH mixture, using S-(-)-α methylbenzylamine and *t*-BDMS-protected R-glycidol as shown in Scheme 46.

Ring opening of S-*t*-BDMS protected glycidol using the S-amine (1 equivalent of amine and epoxide, 1 equivalent of lithium perchlorate, acetonitrile, rt) gave mono protected amino diol (**128**) in 96% yield as a single regioisomer. Cyclisation with phenylphosphonic dichloride (2.2 equivalents of triethylamine, DCM, rt) gave a 1:1 mixture of epimeric oxazaphospholidines (**129**) in 50% yield. Again both were readily separable by flash chromatography. Treatment of either epimer with 1.5 equivalents of phenylmagnesium bromide in THF at -30 °C gave, on warming to room temperature, the phosphinylated amino alcohol (**130**) in 59% yield. Removal of the silyl group using 2 equivalents of TBAF (THF, 0 °C) gave

phosphinamide diol (**127**) in 91% yield as a white foam which was crystallised from diethyl ether/ pentane. This compound was then examined for catalytic activity.



Scheme **46**

(**131**)

Boronate (**131**) was again prepared *in situ* by reaction of a THF solution of (**127**) with BMS at room temperature for 2 hours. Dried acetophenone (see above)

was then added followed by a further equivalent of BMS. This resulted in >98% reduction of starting material in 3 hours at room temperature. The resulting alcohol was obtained in 22% e.e. (S major, 80% yield), which implied that the enantiomer of this compound (i. e. the R, R-diastereoisomer) should give R- selectivity in the reduction. This result seemed somewhat surprising since a 30% d.e. of the R, R-diastereoisomer in a mixture with the R, S- isomer gave overall S- selectivity in the reduction (16% e.e., S major, 84% yield, see above). We believed this may have been due to the superior catalytic activity of the R, S-diastereoisomer in the mixture or a synergic effect occurring between the components of the mixture 'modifying' the active catalytic species.

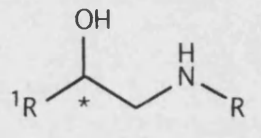
Increasing the concentration of boronate (**108**) appeared to have a detrimental effect on selectivity; use of 1 equivalent of (**108**) in the reaction gave a reduction product of 8% e.e. (S major, 78% yield) which again at first appeared counterintuitive.

It has been presumed that the active catalytic species formed on complexation of the diol with borane are monocyclic and monomeric, though partial association or oligomerisation processes are commonplace in organoborane chemistry.[122] At higher concentrations of diol, monomer-dimer equilibrium (to an unspecified structure) may occur resulting in the formation of a compound with reduced catalytic activity. Such effects have been observed in oxazaborolidine systems.[25,29,98]

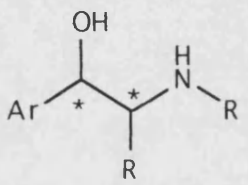
Work is currently underway in the Wills group to optimise reaction conditions for the reduction of acetophenone with borane catalysed by (**108**) and to prepare structural analogues of its precursor (**107**).[124]

Section 2.7: The Use of Phosphinamide N-Protecting Groups for the Intramolecular Directed Reduction of Ketones.[112]

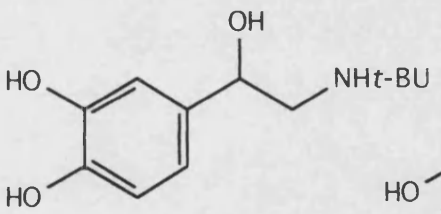
Many important pharmaceutical products and drug candidates are derivatives of chiral amino alcohols. Aryl ethanolamine derivatives of general structure (**132**, R^1=Ar) represent a very important class of β-adrenoreceptor agonists, used in the treatment of asthma, glaucoma and cardiovascular diseases. Examples include Terbutaline (**133**)[99] and Salbutamol (**134**),[100] as well as peptide mimetics such as the enzyme inhibitor Statine (**135**).[101] Preliminary studies on this class of compound has revealed that the isolated enantiomers often show distinctly different biological activities.[102]



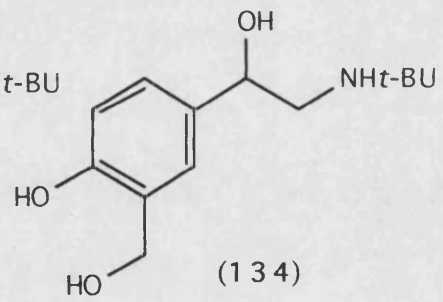
(132)



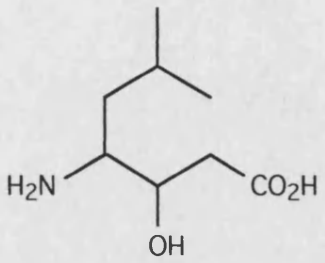
(136) R = R^1 = aryl, alkyl



(133)



(134)

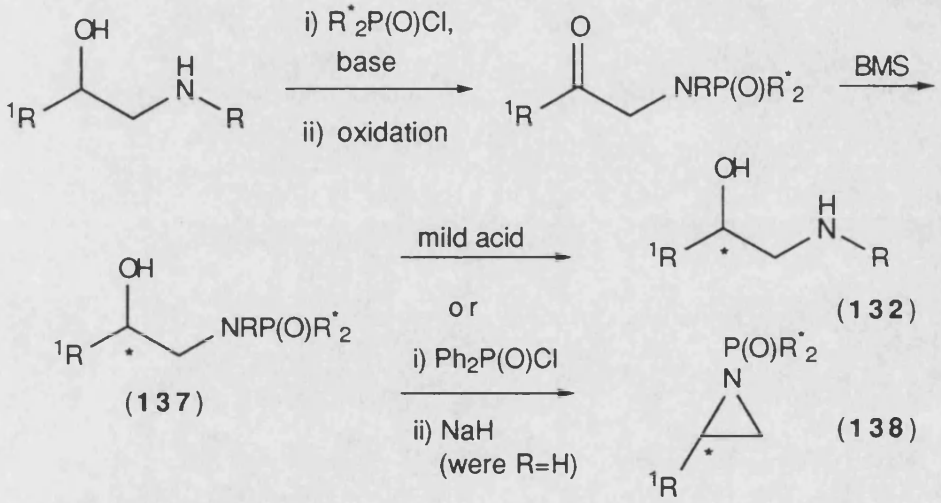


(135)

The current synthetic routes to these materials involve classical resolution or lengthy multi-step synthesis.[100,103] We believed that the inherent

reduction directing ability of the phosphinamides together with their ability to act as an amine protecting group[31,79] would give access to these compounds. The key to this strategy lay in the use of the N-P=O group of an adjacent protected amine to direct the reduction of a neighbouring carbonyl group in an asymmetric[106] (in the case of (**132**)) or diastereoselective[104,105] (in the case of (**136**)) sense.

The ease of introduction and removal of the phosphinyl group[85] make it an ideal candidate as a chiral auxiliary material (see Section 1.2.3) for the control of the asymmetric reduction of proximal ketones and the preparation of aryl ethanolamine targets (Scheme 47).



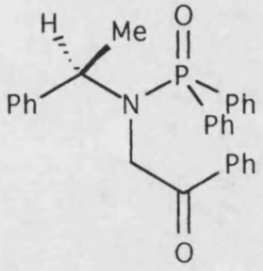
R= H, alkyl, aryl
R*= chiral amine or alkyl group
R^1= alkyl, aryl

Scheme **47**

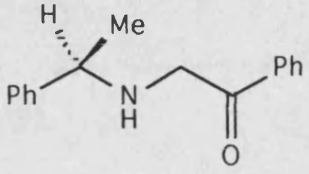
Since secondary amino ketones are prone to facile dimerisation, the proposed route involved protection of an amino alcohol followed by oxidation to give the reduction precursor. Stereoselective reduction would then generate the protected chiral amino alcohol (**137**), which on deprotection would give the homochiral ethanolamine (**132**). Alternatively, cyclisation of the amino alcohol *via* literature procedures would give the corresponding homochiral aziridine (**138**).[79] This protocol could also be applied to the synthesis of diastereomerically pure amino alcohols such as (**136**).

2.7.1 Diastereoselective Reduction.

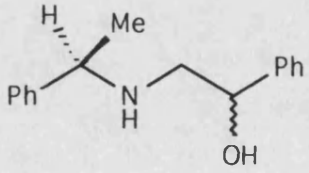
Our initial investigations centred on the preparation of ketophosphinamide (**139**) which we believed would be a suitable model system for examination of reduction diastereoselectivity.



(139)



(140)



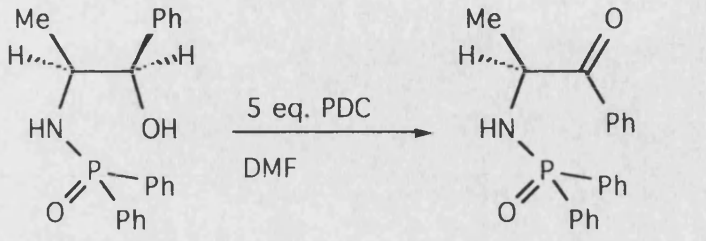
(141)

Attempted preparation of this compound by alkylation of (**29**) (*n*-BuLi, THF, phenacyl chloride) yielded only products arising from ketone deprotonation. The same result was obtained using the corresponding bromide and iodide. Addition of the phosphinyl group as the final step was also considered but attempted preparation of amino ketone (**140**) by reaction of the amine with phenacyl bromide resulted in formation of dimeric products.

Preparation of amino alcohol (**141**) by Lewis acid mediated ring opening of styrene oxide with R-(+)-α methylbenzylamine (1 equivalent of amine, 1 equivalent of lithium perchlorate, acetonitrile, rt) also proved unsuccessful, generating an inseparable mixture of regioisomeric products in low yield. Since the synthesis of (**139**) proved problematic, we turned our attention to norephedrine as a precursor for these studies.

Reaction of 1R, 2S-norephedrine with diphenylphosphinic chloride (1.5

equivalents of triethylamine, DCM, rt) gave the N-phosphinylated amino alcohol (**93**) in 91% yield (see Section 2.6.1). Oxidation of this compound using pyridinium dichromate in DMF[107] (5 equivalents of PDC, rt) gave ketone (**142**) in 90% yield (Scheme 48).



(93) (142), 90%

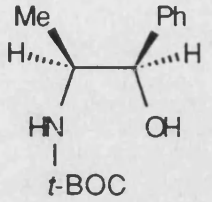
Scheme 48

Similar results were obtained using TPAP/ NMO[108] though problems were encountered with separation of ruthenium residues from the product using this method. Since we were primarily concerned with reduction diastereoselectivity at this stage we were not concerned about possible racemisation of the α- chiral centre.

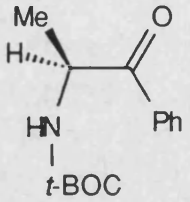
Reduction of ketone (**142**) with BMS (0.6 equivalents of BMS, THF, rt) returned the 1R, 2S product (i.e. (**93**)) in 92% yield as a single diastereoisomer (as assessed by ^{1}H and ^{31}P NMR) in 45 minutes at room temperature.[105] Sodium borohydride reduction of (**142**) (0.25 equivalents of $NaBH_4$, 9:1 EtOH/H_2O) gave amino alcohol (**93**) as an inseperable 2:1 mixture of diastereoisomers (*syn*- major, 90% yield) confirming that the phosphinyl group was not only acting as a nitrogen protecting group but also activating the borane reagent and directing ketone reduction.

Replacing the diphenylphosphinyl group in (**93**) with a *t*-butoxycarbonyl (Boc) group also suggested this was the case. Reaction of 1R, 2S-norephedrine with di-*tert*-butyl dicarbonate (1 equivalent of $(Boc)_2O$, 1.1 equivalents of triethylamine, DCM, rt) gave the *t*-BOC- protected amino alcohol (**143**) in 86% yield.[113] Oxidation of (**143**) with pyridinium dichromate (5 equivalents of PDC, DMF, rt)

gave ketone (**144**) in 70% yield. Reduction of ketone (**144**) with BMS (0.6 equivalents of BMS, THF, rt) afforded the amino alcohol as an inseperable 3.75:1 mixture of diastereoisomers (*syn*-(**143**) major) in 70% yield.



(**143**)



(**144**)

The structure of the transition state for the intramolecular directed reduction is uncertain though it is likely to resemble that shown in Figure 28.

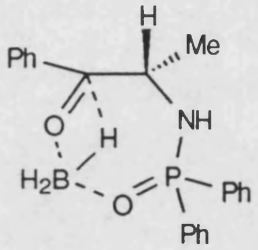
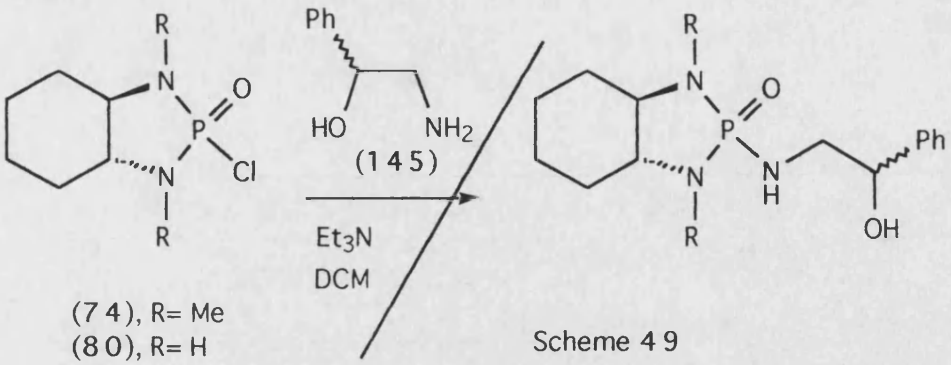


Figure **28**

Co-ordination of the ketone carbonyl group and phosphinyl oxygen atom to borane results in activation of the reducing agent and transfer of hydride can then occur *anti*- to the α methyl group giving the observed product configuration.

2.7.2 Asymmetric Reduction Directed by Remote Chiral Centres.

Encouraged by these results, we next wished to examine asymmetric proximal ketone reduction directed by remote chiral substituents on phosphorus (Scheme 47).



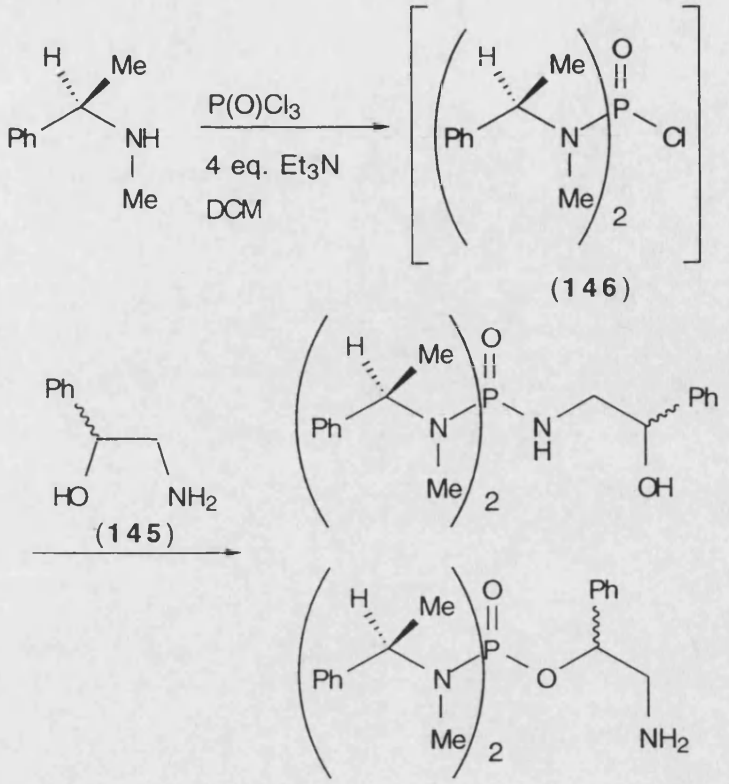
(74), R= Me
(80), R= H

Scheme 49

All attempts to couple amino alcohol (**145**) with cyclic chloride (**74**) proved unsuccessful, presumably due to the inherent lack of reactivity associated with the cyclic electrophile (Scheme 49). Use of the more reactive cyclic phosphoramidic chloride (**80**), generated *in situ* from the corresponding diamine and phosphorus oxychloride (4 equivalents of triethylamine, DCM) resulted only in formation of polymeric baseline materials by TLC.

Reaction of amino alcohol (**145**) with acyclic chloride (**146**), prepared *in situ* by reaction of R-(+)-N-methyl-α methylbenzylamine[46] with phosphorus oxychloride (4 equivalents of triethylamine, DCM), gave an inseparable epimeric mixture of O- and N-phosphinlyated products (as assessed by ^{31}P NMR) (Scheme 50).

This result appeared somewhat surprising since reaction of amino alcohol (**145**) with diphenylphosphinic chloride gave exclusively the N-phosphinylated product (**147**) in 89% yield (1.5 equivalents of triethylamine, DCM). Oxidation of this compound was readily achieved using TPAP/ NMO[108] (1.8 equivalents of NMO, 5 mol% TPAP, 4Å molecular sieve, DCM) to give the corresponding ketone (**148**) in 81% yield.



Scheme **50**

Ketone (**148**) could also be prepared directly in 90% yield by slow addition (over 2 hours) of α-aminoacetophenone hydrochloride to a very dilute solution of excess diphenylphosphinic chloride in DCM at low temperature (1.5 equivalents of diphenylphosphinic chloride (0.04 M), 2.1 equivalents of triethylamine, 0 ^{o}C). No evidence of amino ketone dimerisation was observed under these conditions.

Again cyclic chloride (**74**) appeared to unreactive for this protocol; substrate dimer formation being the dominant reaction. The same problem was also encountered with both chlorides (**80**) and (**146**). In view of these disappointing

results no further studies were undertaken on the coupling reaction.

2.7.3: The Use of Chiral Boronates with Diphenylphosphinyl Protected Amino Ketones.

Since diphenylphosphinyl protected amino ketone (**148**) was in hand, we next considered the use of a catalytic quantity of a suitable chiral boronate (**98**) which in combination with the phosphinamide motif could direct reduction of the proximal keto group (Figure 29).

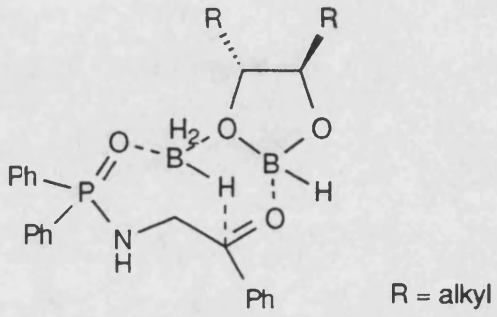


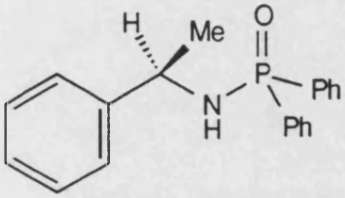
Figure **29**

To this end boronate (**98**, R=Me) was prepared *in situ* by reaction of the diol (**97**, R=Me) with 1.2 equivalents of BMS at room temperature in THF. Addition of ketone (**148**) followed by a further 0.6 equivalents of BMS gave protected amino alcohol (**147**) in 85% yield with complete reduction occurring in 30 minutes at room temperature. The product was, however, obtained in a disappointing 3% e.e. (as assessed by ^{31}P NMR analysis of the corresponding crude Moshers esters).[114]

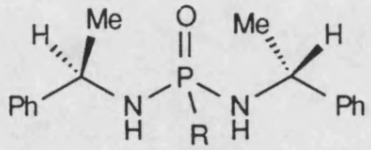
Work is currently underway in the Wills group to couple the dianion of amino alcohol (**145**) with chloride (**74**) and to develop a more efficient route to the requisite phosphinylated ketones.[112]

3 Conclusions.

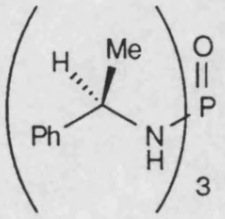
We have identified a novel class of catalysts for the asymmetric reduction of ketones by borane. These are characterised by the presence of an 'N-P=O' (phosphinamide) structural unit which is critical to their activity. The preparation of such compounds is generally trivial involving the reaction of a solution of the appropriate phosphorus chloride with amine in DCM, for example phosphinamide (**29**) prepared in 89% yield from diphenylphosphinic chloride and R-(+)-α methylbenzylamine.



(**29**)



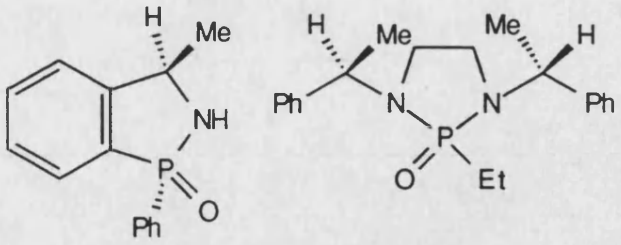
R= Ph (**44**)
R= *i*-Pr (**45**)
R= *t*-Bu (**46**)
R= Cyclopentyl (**47**)



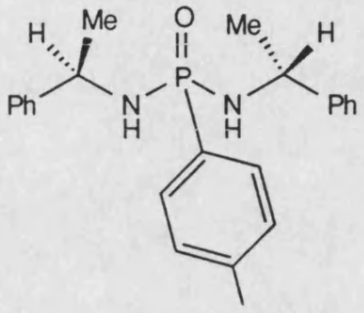
(**43**)

The use of <10 mol% of (**29**) accelerates the reduction of acetophenone with borane by several hundred fold and gives enantiomerically enriched 1-phenylethanol in 26% e.e. Structurally related acyclic phosphonamides of type (**44**)-(**47**) and (**43**) also give similar reduction accelerations, though triphenylphosphine oxide fails to catalyse the reaction.

Examination of conformationally restricted phosphonamides such as (**25**) and (**61**) in the reduction process have demonstrated a clear stereoelectronic requirement for catalysis. Effective electron donation from the nitrogen atom (which is sp^2 hybridised) to the P=O bond requires co-planarity of the full 'R^2N-P=O' unit of the molecule (Figure 14). In this conformation donation from the nitrogen atom to the phosphorus *d*-orbital is presumably permitted. Cyclic systems such as (**25**) and (**61**) are not able to achieve this conformation and are poor reduction catalysts.



(25) (61)

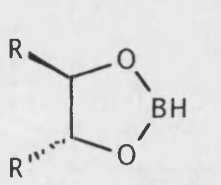


(59)

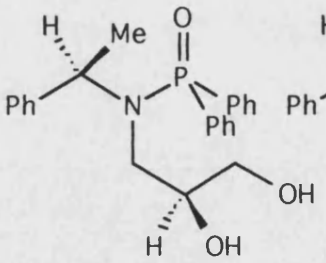
Electron withdrawing substituents on both the nitrogen and phosphorus atoms have a detrimental effect on both the rate of catalysis and asymmetric induction. The presence of an electron donating substituent on phosphorus (e.g. *p*-methoxyphenyl in (**59**)) significantly increases the rate of catalysis, complete reduction of acetophenone occurring in <15 minutes at room temperature in the presence of 5 mol% of (**59**).

On the basis of experimental and theoretical data it is proposed that catalysis is achieved by activation of borane *via* a strong donation from the oxygen atom of the N-P=O system coupled with a much weaker interaction of the carbonyl group lone pair electrons with the phosphorus atom (Figures 13 and 20).

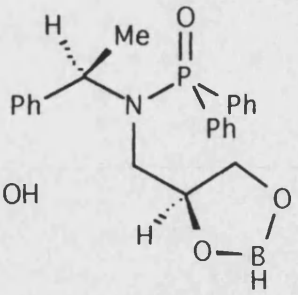
We have also demonstrated that a combination of the phosphinamides together with an electron accepting boronate ester, either as a bi-molecular co-operative system ((**98**) together with (**29**)) or as a single molecular entity (**108**) (prepared *in situ* from phosphinamide diol (**107**) and BMS), significantly improves asymmetric induction, presumably as a consequence of more effective ketone binding.



(98)



(107)



(108)

It has also been demonstrated that the diphenylphosphinyl group is an effective protecting group for primary α-amino ketones and that the resulting ketophosphinamide products are excellent substrates for diastereoselective borane reduction. The diphenylphosphinyl group both activates the borane reagent for hydride transfer and directs the intramolecular reduction.

The development of a novel phosphorus based catalyst for the asymmetric reduction of ketones has been described. A detailed examination of the phosphinamide diol derived catalysts still remains to be carried out together with the synthesis of structural analogues of (**107**). The mechanism of the reduction catalysed by (**108**) is not fully understood and needs further investigation.

If the project is successful then the potential returns will be considerable: a novel, robust and versatile catalyst for a pivotal organic transformation.

4 Experimental.

General Details.

Tetrahydrofuran and diethyl ether were freshly distilled from sodium under an atmosphere of dry nitrogen using benzophenone as an indicator. Toluene was freshly distilled from sodium under a nitrogen atmosphere. Dichloromethane was freshly distilled from phosphorus pentoxide. All solvents were distilled prior to use. Reagents were either used as received from commercial sources or purified by recognised methods.[118] Petroleum ether (petrol) refers to that fraction which boils in the range 60-80 °C.

All reactions, unless otherwise stated, were carried out in flame dried Schlenk tubes under an atmosphere of dry nitrogen or argon.

Flash chromatography[119] was performed using Merck 9835 (70-230 mesh) silica gel. All reactions were monitored by thin layer chromatography (TLC) carried out on aluminium sheets precoated with $60F_{254}$ silica gel, unless otherwise stated, and were visualised by UV light at 254 nm, then potassium permanganate solution, phosphomolybdic acid solution or anisaldehyde solution.

^{1}H-NMR were recorded on a Jeol GX270 FT instrument operating at 270.2 MHz or a Jeol EX400 instrument operating at 399.7 MHz. The observed spectra were for solutions in deuteriochloroform unless otherwise stated. The chemical shifts (δ) were recorded relative to tetramethylsilane as an internal standard; all coupling constants, J, are reported in Hz. ^{13}C-NMR spectra were recorded on a Jeol GX270 FT instrument operating at 67.8 MHz or a Jeol EX400 instrument operating at 100.4 MHz. The spectra were recorded for solutions in deuteriochloroform unless otherwise stated. The chemical shift (δ) were recorded relative to deuteriochloroform (or relative solvent peak) as internal standard in a broad band decoupled mode; the multiplicities were obtained by using 135° and 90° "Distortionless Enhancement by Polarisation Transfer" (DEPT) or Off Resonance Decoupling experiments to aid in assignments (q, methyl; t, methylene; d, methine;

s, quaternary). ^{31}P-NMR spectra were recorded on a Jeol EX400 FT instrument operating at 161.7 MHz using 85% H_3PO_4 as external reference in deuteriochloroform.

Infra red spectra were recorded on a Perkin-Elmer 1600 FT-IR, either as liquid films, evaporated films from chloroform solutions, or as nujol mulls, between sodium chloride plates. Mass spectra were recorded on a VG analytical 7070E instrument with VG2000 data system using either an ionising potential of 70 eV (EI), or by chemical ionisation (isobutane) (CI), or fast atom bombardment (FAB) in 3NBA matrix. High resolution mass measurements (FAB and CI) were recorded by the EPSRC MS service at Swansea. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 141 Polarimeter at ambient temperature. [α] values are reported as 10^{-1}deg cm^2 g^{-1}. Microanalysis was carried out on a Carlo Erba 1106 Elemental Analyser.

HPLC analysis was carried out using a Waters 501 HPLC pump, Waters 486 Tuneable Absorbance Detector and a Waters 746 Data Module (analysis conditions are given in Section 4.1).

Section 4.1: Initial Study.

Preparation of Oxazaphospholidines (26) - (27).

The preparation of diastereomeric oxazaphospholidines (**26**) and (**27**) was based on a literature procedure.[38,62a]

To a stirred solution of 1R, 2S-ephedrine (5.0 g, 0.03 mol) and triethylamine (16.7 cm^3, 0.12 mol) in ethyl acetate (200 cm^3) at 0 °C was added phenylphosphonic dichloride[44] (4.25 cm^3, 0.030 mol) dropwise over 10 minutes. The mixture was allowed to warm to room temperature over 18 hours. It was then poured into an equal volume of saturated ammonium chloride solution and extracted with DCM (3 x 50 cm^3). The combined organic extracts were then dried (magnesium sulfate) and concentrated *in vacuo* to give a colourless solid (7.66 g) consisting of a 1.25:1 mixture of diastereoisomers which were separated on silica eluting with 0→ 50% ethyl acetate- petrol.

Trans-diastereoisomer (**27**): obtained as a white crystalline solid (4.26 g, 50%), Rf 0.65 (ethyl acetate); $[\alpha]_D^{19}$= +36.2 (*c* 1.01, methanol) (lit.,[38] $[\alpha]_D^{22}$= +31.2 (*c* 1, methanol)); δ_H (270 MHz, $CDCl_3$) 0.92 (3 H, d, J 6.4, 4-Me), 2.64 (3 H, d, J 10.1, N-Me), 3.79 (1 H, m, 4-H), 5.62 (1 H, m, 5-H), 7.21-7.62 (8 H, m, aryl H), 7.81-7.92 (2 H, m, aryl H);

Cis-diastereoisomer (**26**): obtained as a white crystalline solid (3.40 g, 40%), Rf 0.45 (ethyl acetate); $[\alpha]_D^{19}$= -33 (*c* 1.14, methanol); δ_H (270 MHz, $CDCl_3$) 0.82 (3 H, d, J 6.6, 4-Me), 2.76 (3 H, d, J 9.3, N-Me), 3.86 (1 H, m, 4-H), 5.99 (1 H, d, J 6.2, 5-H), 7.27-7.60 (8 H, m, aryl H), 7.88-7.96 (2 H, m, aryl H).

Preparation of Oxazaphospholidines (28).

This compound was prepared as a mixture of diastereoisomers by a modified literature procedure.[39]

To a stirred solution of S-prolinol (0.24 cm^3, 2.47 mmol) and triethylamine (0.7 cm^3, 4.95 mmol) in DCM (10 cm^3) at 0 °C was added phenylphosphonic dichloride[44] (0.58 g, 2.47 mmol) dropwise over 5 minutes. The resulting mixture was stirred at 0 °C for 30 minutes then allowed to warm to room temperature and stired for a further 5 hours. It was then poured into an equal volume of saturated aqueous ammonium chloride solution and extracted with DCM (3 x 10 cm^3). The combined organic extracts were dried (magnesium sulfate) and concentrated *in vacuo* to give a pale yellow oil. The crude mixture was then purified by chromatography on silica eluting with 0→2% v/v methanol- DCM. The product was a colourless solid (334 mg, 61%) consisting of a 1.3:1 mixture of diastereoisomers. The following assignments were made by comparison with reported values.[39]

Trans-diastereoisomer: δ_H (270 MHz, $CDCl_3$) 1.52-2.2 (4 H, m, 5-H and 6-H), 2.89 (1 H, m, 4β-H), 3.02 (1 H, m, 4α-H), 4.08 (1 H, m, 8β-H), 4.19 (1 H, br m, 7-H), 4.76 (1 H, dd, J 15 and 4.5, 8α-H) 7.7-7.91 (5 H, m, aryl H); *cis*-diastereoisomer: 1.72-2.21 (4 H, m, 5-H and 6-H), 2.97 (1 H, m, 4β-H), 3.77 (1 H, m, 4α-H), 3.92 (1 H, ddd, J 8.5, 8 and 3.5, 8β-H), 4.15 (1 H, br m, 7-H), 4.35 (1 H, m, 8α-H) 7.41-7.62 (5 H, m, aryl H).

Preparation of R-(+)-(N-phenethyl)-diphenylphosphinamide (29).

To a solution of (R)-(+)-α methylbenzylamine (0.54 cm^3, 4.2 mmol) and triethylamine (1.2 cm^3, 8.4 mmol) in DCM (20 cm^3) was added diphenylphosphinic chloride (0.81 cm^3, 4.2 mmol) dropwise at 0 °C. The resulting mixture was stirred at room temperature overnight. It was then poured into an equal volume of saturated aqueous ammonium chloride solution and extracted with DCM (3 x 10 cm^3). The combined organic extracts were dried (sodium sulfate) and concentrated *in vacuo* to give phosphinamide (**29**) as a colourless solid which was purified by recrystallisation from DCM/ hexane (1.20g, 89%), m. p 158-162 °C

(d) (found: C, 74.7; H, 6.2; N, 4.3. $C_{20}H_{20}NPO$ requires C, 74.77; H, 6.23; N, 4.36%); $[\alpha]_D^{22}$= +40.2 (*c* 1.0, Methanol); υ_{max} (nujol)/ cm^{-1} 1961, 1902, 1671, 1307, 1204, 1172, 1108, 1034, 968, 742 and 542; δ_H (400 MHz, $CDCl_3$) 1.53 (3 H, d, J 6.7, $CHCH_3$), 3.23 (1 H, br m, NH), 4.35 (1 H, br q, J 6.7, $CHCH_3$), 7.18-7.84 (11 H, m, aryl H), 7.76-7.90 (4 H, m, aryl H); δ_C (68 MHz, $CDCl_3$), 25.9 (dq, J_{PC} 3.3), 51.0 (d), 125.9, 127.0, 128.2, 128.3, 128.4, 128.5, 131.8, 131.9, 132.3, 132.4, 145.0 (dd, J_{PC} 6.6); δ_P (162 MHz, $CDCl_3$) 22.4 (1 P, s); *m/z* (EI) 321 (M^+, 4%), 306 (30), 201 (70), 120 (100), 106 (60), 77 (50), 57 (50), 43 (50).

General Reduction Procedure.

The following procedure describes the initial activity screen for phosphinamide (**29**) and is typical (reaction times, yields and selectivities for related systems are described in the text). The same general procedure was adopted for all ketone substates.

To a stirred solution of phosphinamide (**29**) (10 mol%, 82 mg, 0.257 mmol) and acetophenone (0.3 cm^3, 2.57 mmol) in anhydrous THF (2.5 cm^3) was added BMS (10 M dimethyl sulfide complex, 0.15 cm^3, 1.54 mmol) dropwise over 2 minutes. Vigorous effervescence was observed. The mixture was then stirred at room temperature for 1 hour (or until all of the ketone was consumed by TLC. The mixture was then diluted with diethyl ether and saturated aqueous ammonium chloride solution (1 cm^3) added dropwise. The organic phase was then separated and the aqueous layer extracted with diethyl ether (3 x 5 cm^3). The combined extracts were then dried (sodium sulfate) and concentrated *in vacuo*. The catalyst was then removed by chromatography on silica, eluting with 20% v/v ethyl acetate-petrol. This gave 1-phenylethanol as a colourless oil which was further purified by distillation under reduced pressure (257 mg, 82%), b. p 44 °C / 0.5 mmHg (lit.,[40] 98 °C / 20 mmHg); $[\alpha]_D^{23}$= -11.5 (*c* 1, methanol), 26% e. e. (S- enantiomer)[40]; δ_H

(270 MHz, $CDCl_3$) 1.47 (3 H, d, J 6, $CHCH_3$), 2.15 (1 H, br s, OH), 4.85 (1 H, q, J 6, $CHCH_3$), 7.22-7.37 (5H, m, aryl H).

The enantiomeric excess was confirmed by chiral HPLC analysis.

HPLC Conditions:

Separation of Acetophenone and 1-Phenylethanol:

Column:	Techspere 5 ODS C18.
Eluent:	37% acetonitrile/ water.
Flow rate:	2 cm^3min^{-1}
Injection:	5 µl
Temperature:	Ambient.
Detection:	UV at λ= 254 nm.
Retention times:	Acetophenone: 2.7 min.
	1-Phenylethanol: 2.05 min.

Separation of R- and S- 1-Phenylethanol Enantiomers:

Column:	CHIRAL CEL OD.
Eluent:	8% isopropyl alcohol/ hexane, 0.1% diethylamine.
Flow rate:	0.5 cm^3min^{-1}
Injection:	10 µl
Temperature:	Ambient.
Detection:	UV at λ= 254 nm.
Retention times:	(R)-(+)-1-phenylethanol: 10.9 min.
	(S)-(-)-1-phenylethanol: 11.9 min.

Section 4.2: Modification of the Basic Phosphinamide Structure.

*Preparation of R-(+)-(N-methyl)(N-1-phenethyl)-diphenylphosphinamide (**40**).*

To a stirred solution of R-(+)-(N-phenethyl)-diphenylphosphinamide (**29**) (0.5 g, 1.56 mmol) in anhydrous THF (25 cm^3) at 0 °C was added *n*-butyllithium (1.6 M hexane solution, 1.08 cm^3, 1.73 mmol) dropwise. The resulting pale yellow solution was stirred at 0 °C for a further 45 minutes. Methyl iodide (0.1 cm^3, 1.56 mmol) was then added and the mixture allowed to warm to room temperature overnight. It was then poured into an equal volume of saturated aqueous ammonium chloride solution and extracted with DCM (3 x 10 cm^3). The combined organic extracts were dried (sodium sulfate) and concentrated *in vacuo* to afford phosphinamide (**40**) as a pale yellow oil. This was then purified on silica eluting with 0→30% v/v ethyl acetate- petrol (303 mg, 58%), m. p. 114-117 °C (from DCM/ hexane), (found C, 75.5; H, 6.3; N, 4.2. $C_{21}H_{22}NOP$ requires C, 75.22; H, 6.67; N, 4.18%); $[\alpha]_D^{22}$= +49.9 (*c* 1.0, methanol); υ_{max} (nujol)/ cm^{-1} 3014, 1539, 1493, 1438, 1179, 1122, 982, 932, 698 and 666; δ_H (400 MHz, $CDCl_3$) 1.52 (3 H, d, J 7, CHC*H*$_3$), 2.28 (3 H, d, J 10.7, N-Me), 4.65 (1 H, dq, J 8.9 and 7.8, C*H*CH$_3$), 7.27-7.42 (10 H, m, aryl H), 7.8-7.85 (5 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 16.9 (q), 27.7 (dq, J_{PC} 4.4), 53.1 (dd, J_{PC} 3.3), 126.9, 127.6, 128.1, 128.3, 128.5, 131.6, 132.16, 132.2, 132.3, 132.8, 133.1, 141.0 (dd, J_{PC} 5.5); δ_P (162 MHz, $CDCl_3$) 30.7 (1 P, s); *m/z* (CI) 336 (M^++1, 100%), 320 (4), 232 (5), 203 (15), 134 (35).

*R-(+)-(N-benzyl)(N-1-phenethyl)-diphenylphosphinamide (**41**).*

This compound was prepared according to the above procedure using benzyl bromide (0.19 cm^3, 1.56 mmol). Phosphinamide (**41**) was isolated as a white solid (256 mg, 40%), m. p. 114-117 °C (from DCM/ hexane), (found C, 78.7; H, 6.3; N, 3.2. $C_{27}H_{26}NOP$ requires C, 78.83; H, 6.33; N, 3.41%); $[\alpha]_D^{20}$= -2 (*c* 1.0, methanol); υ_{max} (nujol)/ cm^{-1} 2924, 1378, 1198, 1119, 1099, 1022, 880, 748 and

695; δ_H (270 MHz, $CDCl_3$) 1.32 (3 H, d, J 7.1, CHC*H*$_3$), 3.80 (1 H, dd, J 14 and 11.4, C*H*$_2$), 4.11 (1 H, dd, J 14 and 11.7, C*H*$_2$), 4.67 (1 H, dq, J 9.75 and 7.2, C*H*CH$_3$), 6.94-7.13 (4 H, m, aryl H), 7.14-7.39 (12 H, m, aryl H), 7.81-7.9 (4 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 19.9 (dq, J_{PC} 3.3), 47.5 (dt, J_{PC} 3.3), 55.3 (dd, J_{PC}, 4.3), 126.7, 127.3, 127.9, 128.1, 128.2, 128.25, 128.3, 128.4, 128.5, 128.6, 131.5, 131.6, 131.65, 132.5, 132.65, 132.7, 139.6, (dd, J_{PC} 3.3), 140.8 (dd, J_{PC} 4.4); δ_P (162 MHz, $CDCl_3$) 31.2 (1 P, s); *m/z* (CI) 412 (M^++1, 100%), 320 (32), 306 (17), 201 (11), 91 (8).

Preparation of Acyclic *C2* Symmetric Phosphonamides.

a) General Procedure from Phosphonic Dichlorides:

The following procedure is typical.

*Preparation of R, R-(+)-(N, N'-di-1-phenethyl) phenyl phosphonamide (**44**).*

To a stirred solution of R-(+)-α methylbenzylamine (5.3 cm^3, 41 mmol) and triethylamine (6.4 cm^3, 46 mmol) in DCM (80 cm^3) at 0 °C was added phenylphosphonic dichloride[44] (2.91 cm^3, 21 mmol) dropwise over 10 minutes. The cloudy solution was allowed to warm to room temperature and stirred overnight. The mixture was then poured into an equal volume of saturated aqueous ammonium chloride solution and extracted with DCM (3 x 15 cm^3). The combined organic extracts were dried (magnesium sulfate) and concentrated *in vacuo*. The residue was then purified on silica eluting with 0→50% v/v ethyl acetate- petrol. This afforded phosphonamide (**44**) as a white foam (6.71 g, 45%), m. p. 65-67 °C (from DCM/ hexane), (found C, 71.7; H, 7.0; N, 7.4. $C_{22}H_{25}N_2OP$ requires C, 72.52; H, 6.87; N, 7.68%); $[\alpha]_D^{20}$= +41.1 (*c* 1.0, methanol); υ_{max} (nujol)/ cm^{-1} 1376, 1208, 1180 and 1126; δ_H (400 MHz, $CDCl_3$) 1.33 (3 H, d, J 6.7, CHC*H*$_3$), 1.41 (3 H, d, J 6.7, CHC*H*$_3$), 2.69 (1 H, br t, J 8.5, NH), 2.83 (1 H, brt, J 9.5, NH),

4.31 (1 H, m, C*H*CH3), 4.56 (1 H, m, C*H*CH3), 7.05-7.44 (13 H, m, aryl H), 7.71 (2 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 25.5 (dq, J_{PC} 4.4), 25.9 (q), 50.2 (d), 50.8 (d), 125.8, 126.8, 127.0, 128.1, 128.3, 128.35, 128.6, 131.7, 131.8, 145.1, 145.2 (d, J_{PC} 5.6), 145.8 (d, J_{PC} 5.5); δ_P (162 MHz, $CDCl_3$) 19.0 (1 P, s); *m/z* (CI) 365 (M^++1, 100%), 349 (10), 120 (25), 105 (15), 89 (52).

*R, R-(+)-(N, N'-di-1-phenethyl) ethyl phosphonamide (**42**).*

This compound was prepared according to the above general procedure using R-(+)-α-methyl benzylamine (6.2 cm^3, 46.8 mmol), triethylamine (7.31 cm^3, 52.5 mmol) and ethylphosphonic dichloride (2.56 cm^3, 24 mmol) in DCM (70 cm^3). Phosphonamide (**42**) was isolated as a viscous oil which solidified on standing (9.61g, 65%), m. p. 65-66 °C (from DCM/ hexane), (found C, 68.1; H, 8.0; N, 8.8. $C_{18}H_{25}N_2OP$ requires C, 68.33; H, 7.96; N, 8.85%); $[\alpha]_D^{22}$ = +72.6 (*c* 1.05, methanol); υ_{max} (nujol)/ cm^{-1} 3216, 1460, 1374, 1203, 1167, 1125 and 1087; δ_H (270 MHz, $CDCl_3$) 0.95 (6 H, dt, J 18.6 and J 7.7, CH_2CH_3), 1.36 (3 H, d, J 7, $CHCH_3$), 1.47 (3 H, d, J 6.8, $CHCH_3$), 2.43 (1 H, br t, J 10.5, NH), 2.70 (1 H, br t, J 10.2, NH), 4.38 (1 H, m, C*H*CH3), 4.45 (1 H, m, C*H*CH3), 7.2-7.31 (10 H, m. aryl H); δ_C (68 MHz, $CDCl_3$) 6.7 (dq, J_{PC} 5.5), 21.9 (dt, J_{PC} 114), 25.6 (dq, J_{PC} 5.5), 26.1 (dq, J_{PC} 5.5), 50.0 (d), 50.2 (d), 125.6 (d), 125.7 (d), 126.8 (d), 126.9 (d), 128.4 (d), 128.5 (d), 145.6 (d, J_{PC} 3.25), 145.8 (d, J_{PC} 4.3); δ_P (162 MHz, $CDCl_3$) 33.7 (1 P, s); *m/z* (CI) 317 (M^++1), 100%), 301 (10), 120 (22), 105 (13).

*Phosphinamide Chloride (**48**).*

Reaction of *t*-butlyphosphonic dichloride (1.52 g, 8.68 mmol) with R-(+)-α methyl benzylamine (2.24 cm^3, 17.4 mmol) and triethylamine (2.66 cm^3, 19.1 mmol) in DCM (25 cm^3) according to the above general procedure gave, unexpectedly, the phosphinamide chloride (**48**) as an inseparable 1.6:1 mixture of

diastereoisomers (883 mg, 39%) , (found C, 55.3; H, 7.4; N, 5.3. $C_{12}H_{19}NOPCl$ requires C, 55.49; H, 7.37; N, 5.39%); υ_{max} (nujol)/ cm^{-1} 3215, 2971, 1476, 1450, 1398, 1370, 1232, 1200, 1116, 1081, 1038, 972, 762 and 701; δ_H (400 MHz, $CDCl_3$) major diastereoisomer: 1.28 (9 H, d, J 19.8, CMe_3), 1.55 (3 H, d, J 6.8, $CHCH_3$), 3.21 (1 H, br m, NH), 4.72 (1 H, m, $CHCH_3$), 7.25-7.38 (5 H, m, aryl H); minor diastereoisomer: 1.24 (9 H, d, J 20, CMe_3), 1.62 (3 H, d, J 7, $CHCH_3$), 3.16 (1 H, br m, NH), 4.84 (1 H, m, $CHCH_3$), 7.25-7.38 (5 H, m, aryl H);δ_C (68 MHz, $CDCl_3$) major diastereoisomer: 24.1 (q), 24.4 (q), 24.9 (d, J_{PC} 6.6), 51.3 (dd, J 3.3), 126.1 (d), 127.5 (d), 128.7 (d), 144.2 (s); major diastereoisomer: 24.0 (q), 24.44 (q), 24.9 (d, J_{PC} 6.6), 50.4 (dd, J_{PC} 4.4), 126.0 (d), 127.4 (d), 128.6 (d), 143.9 (d, J_{PC} 4.3); δ_P (162 MHz, $CDCl_3$) major diastereoisomer: 58.5 (1 P, s); minor diastereoisomer: 58.2 (1 P, s); *m/z* (CI) 262 (M^++1, 30%), 260 (M^++1, 100%), 224 (5), 202 (10), 156 (6), 120 (21).

*R, R, R-(+)-(N, N', N"-tri-1-phenethyl) phosphoramide (**43**).*

This compound was prepared according to the above general procedure using R-(+)-α methylbenzylamine (1.25 cm^3, 9.72 mmol), triethylamine (1.35 cm^3, 9.72 mmol) and phosphorus oxychloride (0.3 cm^3, 3.24 mmol) in DCM (15 cm^3). Phosphoramide (**43**) was isolated as a colourless solid (1.05 g, 80%), m. p. 104-107 °C (from DCM/ hexane); (found C, 70.4; H, 7.4; N, 10.3. $C_{24}H_{30}N_3OP$ requires C, 70.76; H, 7.37; N, 10.32%); $[\alpha]_D^{19}$= +23.1 (*c* 1.74, chloroform); υ_{max} (nujol)/ cm^{-1} 3215, 1601, 1455, 1375, 1204, 1170, 1108, 1072, 980, 878, 744 and 699; δ_H (400 MHz, $CDCl_3$) 1.31 (9 H, d, J 6.8, $CHCH_3$), 2.45 (3 H, br t, J 8, NH), 4.31 (3 H, m, $CHCH_3$), 7.12-7.27 (15 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 25.6 (dq, J_{PC} 5.6), 51.0 (d), 125.8 (d), 126.9 (d), 128.5 (d), 145.7 (d, J_{PC} 3.3); δ_P (162 MHz, $CDCl_3$) 11.9 (1 P, s); *m/z* (EI) 407 (M^+, 40%), 392 (40), 302 (31), 287 (10), 120 (40), 106 (100).

b) General Procedure by Reaction of Chloride (49) with a Grignard Reagent:

The following procedure is typical.

Preparation of R, R-(+)-(N, N'-di-1-phenethyl) isopropyl phosphonamide (45)

To a stirred solution of R-(+)-α methylbenzylamine (1.7 cm^3, 13 mmol) and triethylamine (1.81 cm^3, 13 mmol) in DCM (20 cm^3) at 0 °C was added phosphorus oxychloride (0.61 cm^3, 6.5 mmol) dropwise over 5 minutes. The resulting cloudy mixture was allowed to warm slowly to room temperature and stirred for a further 8 hours. The solvent was then removed *in vacuo* and the residue extracted with anhydrous ethyl acetate. The solution was filtered to remove hydrochloride salts and again concentrated *in vacuo* to give chloride (**49**) as a viscous pale yellow oil which decomposed slowly at room temperature:
δ_H (270 MHz, $CDCl_3$) 1.33 (3 H, d, J 6.8, $CHCH_3$), 1.42 (3 H, d, J 6.6, $CHCH_3$), 3.41-3.69 (2 H, br s, NH), 4.37 (2 H, m, $CHCH_3$), 7.08-7.29 (10 H, m, aryl H); *m/z* (CI) 325 (M^++1, 0.3%), 323 (M^++1, 1%), 147 (5), 105 (100).

The chloride was immediately redissolved in anhydrous diethyl ether (12 cm^3) and the solution cooled to 0°C. Isopropylmagnesium chloride[47] (2 M diethyl ether solution, 4 equivalents, 13 cm^3, 26 mmol) was then added dropwise over 10 minutes. The cloudy mixture was stirred at 0 °C for 1 hour, then warmed slowly to room temperature and stirred for a further 3 hours (or until all chloride was consumed by TLC). The mixture was then poured into an equal volume of saturated aqueous ammonium chloride solution and extracted with DCM (3 x 10 cm^3). The combined organic extracts were dried (magnesium sulfate) and concentrated *in vacuo*. The residue was then purified on silica eluting with 0→5% v/v methanol- DCM to afforded phosphonamide (**45**) as a colourless solid (1.39 g, 65%), m. p. 35-38 °C; $[\alpha]_D^{18}$= +24.0 (*c* 0.15, chloroform); υ_{max} (nujol)/ cm^{-1} 3402, 3200, 1392, 1276, 1124, 967, 867, 761 and 699; δ_H (270MHz, $CDCl_3$) 0.86 (3 H,

dd, J 17.2 and 7.1, (CH_3)$_2$CH), 0.99 (3 H, dd, J 17 and 7.3, (CH_3)$_2$CH), 1.22 (3 H, d, J 6.9, CHCH_3), 1.41 (3 H, d, J 6.8, CHCH_3), 1.62 (1 H, m, (CH_3)$_2$CH), 2.19 (1 H, br t, J 10, NH), 2.60 (1 H, m, NH), 4.3-4.35 (1 H, m, CHCH$_3$), 4.4-4.42 (1 H, m, CHCH$_3$), 7.04-7.28 (10 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 16.4 (dq, J_{PC} 3.3), 16.7 (dq, J_{PC} 4.4), 26.0 (dq, J_{PC} 4.4), 26.4 (dq, J_{PC} 5.5), 27.9 (dd, J_{PC} 115), 49.5 (d), 50.3 (d), 125.6 (d), 125.7 (d), 126.75 (d), 126.9 (d), 128.4 (d), 128.6 (d), 146.0 (d, J_{PC} 4.4), 146.2 (d, J_{PC} 3.25; δ_P (162 MHz, $CDCl_3$) 33.7 (1 P, s); *m/z* (CI) 331 (M^++1, 100%), 315 (11), 120 (20), 105 (19); (found $[M+H]^+$, 331.1936. $C_{19}H_{28}N_2OP$ requires *m/z*, 331.1939).

R, R-(+)-(N, N'-di-1-phenethyl) phenyl phosphonamide (44)

This compound was prepared according to the above general procedure using phenylmagnesium bromide.[47] Phosphonamide (**44**) was isolated as a viscous oil which solidified on standing (1.06 g, 45%); data as above.

R, R-(+)-(N, N'-di-1-phenethyl) ethyl phosphonamide (42)

This compound was prepared according to the above general procedure using ethylmagnesium chloride.[47] Phosphonamide (**42**) was isolated as a viscous oil which solidified on standing (863 mg, 42%); data as above.

R, R-(+)-(N, N'-di-1-phenethyl) cyclopentyl phosphonamide (47).

This compound was prepared according to the above general procedure using chloride (**49**) (200 mg, 0.62 mmol) and cyclopentylmagnesium chloride (2 M diethyl ether solution, 0.94 cm^3, 1.88 mmol) in anhydrous diethyl ether (10 cm^3). Phosphonamide (**47**) was isolated as a colourless oil (72 mg, 33%), $[\alpha]_D^{18}$= +41.1 (*c* 0.18, chloroform); υ_{max} (film)/ cm^{-1} 3219, 2967, 1453, 1373, 1208, 1146, 994,

912, 761 and 700; δ_H (270 MHz, $CDCl_3$) 1.13 (3 H, d, J 7, $CHCH_3$), 1.15-1.61 (12 H, m, alkyl H), 2.3 (1 H, m, NH), 2.46 (1 H, m, NH), 4.23-5.2 (2 H, m, $CHCH_3$), 7.09-7.23 (10 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 22.9 (dt, J_{PC} 5.5), 25.4 (dq, J_{PC} 5.5), 26.0 (dq, J_{PC} 4.4), 26.4 (t), 27.2 (t), 33.9 (dt, J_{PC} 4.4), 37.7 (dd, J_{PC} 118), 49.8 (d), 51.1 (d), 125.6 (d), 125.7 (d), 125.75 (d), 126.7 (d), 126.8 (d), 128.3 (d), 128.4 (d), 128.5 (d), 145.9 (s), 146.1 (d, J_{PC} 3.3); δ_P (162 MHz, $CDCl_3$) 10.9 (1 P, s); *m/z* (CI) 357 (M^++1, 100%), 341 (12), 305 (14), 120 (22), 105 (21); (found $[M+H]^+$, 357.2101. $C_{21}H_{30}N_2OP$ requires *m/z*, 357.2096).

R, R-(+)-(N, N'-di-1-phenethyl)(p-methoxyphenyl) phosphonamide (59).

This compound was prepared according to the above general procedure using chloride (**49**) (1.0 g, 3.1 mmol) and p-methoxyphenylmagnesium bromide[47] (0.25 M diethyl ether solution, 3 equivalents, 37.2 cm^3, 9.3 mmol) in anhydrous diethyl ether (50 cm^3). Phosphonamide (**47**) was isolated as a colourless oil (500 mg, 41%), $[\alpha]_D^{12}$ = +29.5 (*c* 1.3, chloroform); υ_{max} (film)/ cm^{-1} 3212, 3028, 2970, 1598, 1494, 1454, 1382, 1294, 1205, 1120, 967, 831, 760 and 899; δ_H (270 MHz, $CDCl_3$) 1.53 (3 H, d, J 7, $CHCH_3$), 1.61 (3 H, d, J 6.8, $CHCH_3$), 2.84 (1 H, m, NH), 2.94 (1 H, m, NH), 4.02 (3 H, s, MeO), 4.4-4.62 (2H, m, $CHCH_3$), 7.05 (2 H, dd, J 9 and 3, aryl H), 7.25-7.53 (10 H, m, aryl H), 7.85 (2 H, dd, J 12.8 and 8, aryl H); δ_C (68 MHz, $CDCl_3$) 25.2 (q), 25.3 (q), 49.8 (d), 50.3 (d), 54.8 (q), 113.2 (dd, J_{PC} 14.3), 125.5 (d), 125.54 (d), 126.4 (d), 126.5 (d), 127.9 (d), 128.0 (d), 128.1 (d), 133.3 (dd, J_{PC} 10.9), 145.5 (s), 145.6 (d, J_{PC} 3.3), 161.6 (d, J_{PC} 3.4); δ_P (162 MHz, $CDCl_3$) 18.7 (1 P, s); *m/z* ((-) FAB) 393 (M^+-1, 100%), 331 (54), 303 (50), 182 (21); (found $[M-H]^+$, 393.1725. $C_{23}H_{26}N_2O_2P$ requires *m/z*, 393.1732).

Preparation of R, R-(+)-(N, N'-di-1-phenethyl) t-butyl phosphonamide (46).

To a stirred solution of R-(+)-α methylbenzylamine (0.1 cm^3, 0.74 mmol) in anhydrous THF (9 cm^3) at 0 °C was added *n*-butyllithium (2.4 M hexane solution, 0.31 cm^3, 0.74 mmol) dropwise over 2 minutes. The resulting pale yellow solution was stirred at 0 °C for 30 minutes. A THF solution of chloride (**48**) (97 mg, 0.37 mmol) was then added, the mixture warmed slowly to room temperature and stirred for a further 6 hours. An equal volume of saturated aqueous ammonium chloride solution was then added and the product extracted with DCM (3 x 5 cm^3). The combined organic extracts were dried (sodium sulfate) and concentrated *in vacuo*. The residue was purified on silica eluting with 0→5% v/v methanol- DCM to afford phosphonamide (**46**) as colourless solid (103 mg, 81%), (found C, 68.9; H, 8.6; N, 7.6. $C_{20}H_{29}N_2OP$. ¼ H_2O requires C, 68.87; H, 8.46; N, 8.03%); $[\alpha]_D^{20}$= +22.5 (*c* 0.19, chloroform); υ_{max} (nujol)/ cm^{-1} 3225, 2871, 1494, 1455, 1207 and 996; δ_H (270 MHz, $CDCl_3$) 1.04 (9 H, d, J 15.4, CMe_3), 1.23 (3 H, d, J 6.8, $CHCH_3$), 1.5 (3 H, d, J 6.8 $CHCH_3$), 2.04 (1 H, br t, J 9, NH), 2.52 (1 H, m, NH), 4.41 (1 H, m, $CHCH_3$), 4.60 (1 H, dq, J 12 and 7.5, $CHCH_3$), 7.07-7.39 (10 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 25.3 (q), 26.6 (q), 32.4 (d, J_{PC} 117.7), 26.7 (q), 49.4 (dd, J_{PC} 2.2), 50.7 (d), 125.6 (d), 125.65 (d), 126.6 (d), 126.9 (d), 128.4 (d), 128.7 (d), 146.1 (s), 146.6 (d, J_{PC} 3.3); δ_P (162 MHz, $CDCl_3$) 36.2 (1 P, s); *m/z* (CI) 345 (M^++1, 100%), 329 (15), 287 (7), 120 (15), 105 (20).

Preparation of Catalysts Chiral at Phosphorus.

Preparation of Epimeric Phosphonamides (50).

To a stirred solution of R, R-(+)-(N, N'-di-1-phenethyl)phenyl phosphonamide (**44**) (2.0 g, 5.5 mmol) in anhydrous THF (100 cm^3) at 0 °C was

added *n*-butyllithium (2.2 M hexane solution, 2.5 cm^3, 5.5 mmol) dropwise over 10 minutes. The resulting pale yellow solution was stirred for a further 1 hour. Benzyl bromide (0.95 cm^3, 7.7 mmol) was added and the mixture warmed to room temperature and stirred for 24 hours. It was then poured into a saturated aqueous ammonium chloride solution (50 cm^3) and extracted with ethyl acetate (3 x 50 cm^3). The combined organic extracts were washed with saturated aqueous brine (30 cm^3), dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on silica eluting with 0→40% v/v ethyl acetate- petrol. This afforded phosphonamide (**50**) as a colourless solid consisting of a 1:1 mixture of epimers (1.02 g, 41%). Pure samples of both epimers were obtained by preparative TLC (60 mg of mixture repeatedly eluted with 30% v/v ethyl acetate- petrol). The prefix 'upper' and 'lower' refers to elution order (**50U** being the least polar and **50L** the more polar compound).

Upper diastereoisomer (**50U**): m. p. 92-95 °C (from DCM/ hexane); (found C, 76.2; H, 7.0; N, 6.0. $C_{29}H_{31}N_2OP$ requires C, 76.65; H, 6.83; N, 6.17%); $[\alpha]_D^{18}$= -25.6 (*c* 0.18, chloroform); υ_{max} (nujol)/ cm^{-1} 3150, 1178, 1133, 1116, 1028, 966, 923, 743 and 696; δ_H (400 MHz, $CDCl_3$) 1.24 (3 H, d, J 7, CHC*H*$_3$), 1.33 (3 H, d, J 6.7, CHC*H*$_3$), 2.42 (1 H, br m, NH), 3.70 (1 H, dd, J 16 and 11.6, C*H*$_2$Ph), 4.12-4.22 (2 H, m, C*H*$_2$Ph and C*H*CH$_3$), 5.09 (1 H, dq, J 10 and 7, C*H*CH$_3$), 6.73-6.79 (2 H, m, aryl H), 6.93-6.95 (2 H, m, aryl H), 7.04-7.47 (14 H, m, aryl H), 7.61-7.84 (2 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) 18.4 (q), 25.2 (q), 46.2 (dt, J_{PC} 3.7), 50.5 (d), 53.6 (dd, J_{PC} 5.5), 125.8, 126.7, 127.0, 127.5, 127.9, 128.0, 128.2, 128.4, 131.2, 132.0, 132.1, 132.3, 132.8, 140.0, 141.8 (d, J_{PC} 3.6), 145.0 (d, J_{PC} 5.5); δ_P (162 MHz, $CDCl_3$) 24.8 (1 P, s); *m/z* (CI) 455 (M^++1, 50%), 391 (92), 279 (42), 167 (34), 149 (100), 113 (45).

Lower diastereoisomer (**50L**): (found C, 76.4; H, 6.7; N, 5.9. $C_{29}H_{31}N_2OP$ requires C, 76.65; H, 6.83; N, 6.17%); $[\alpha]_D^{18}$= +12.8 (*c* 0.21, chloroform); υ_{max} (nujol)/ cm^{-1} 3150, 1178, 1132, 1110, 1028, 960, 928, 743 and 689; δ_H (400 MHz, $CDCl_3$) 1.18 (3 H, d, J 7, CHC*H*$_3$), 1.39 (3 H, d, J 7, CHC*H*$_3$), 2.55 (1 H, br t, J 8,

NH), 3.9-4.11 (2 H, m, C*H*$_2$Ph), 4.34 (1 H, m, C*H*CH$_3$), 4.73 (1 H, dq, J 10 and 6.4, C*H*CH$_3$), 6.79-6.85 (2 H, m, aryl H), 7.01-7.25 (12 H, m, aryl H), 7.36-7.48 (4 H, m, aryl H), 7.76 (2 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 19.1 (q), 25.3 (q), 46.9 (dt, J_{PC} 3.6), 50.1 (d), 54.4 (dd, J_{PC} 3.6), 125.9, 126.7, 126.85, 127.1, 127.6, 127.9, 128.1, 128.2, 128.4, 131.4, 131.45, 132.1, 132.3, 141.7, 144.7, 145.3; δ_P (162 MHz, $CDCl_3$) 23.5 (1 P, s); *m/z* (CI) 455 (M^++1, 100%), 391 (22), 363 (55), 349 (26), 149 (46), 113 (27), 105 (56).

Diastereomerically Pure Phosphinamides.

General Procedure from Chloride (55):

The following procedure is typical.

Preparation of (1R)-N-(1-Phenethyl)-(R$_P$)-P-phenyl-P-(2,4,6- trimethylphenyl) phosphinamide (52).

To a stirred solution of phenylphosphonic dichloride (1.1 cm^3, 7.76 mmol) in DCM (15 cm^3) at -78 °C was added a solution of R-(+)-α methylbenzylamine (1.0 cm^3, 7.76 mmol) and triethylamine (1.08 cm^3, 7.76 mmol) in DCM (6 cm^3) dropwise over 10 minutes. The resulting solution was allowed to warm slowly to room temperature and stirred for 10 hours. The mixture was then concentrated *in vacuo* and the residue extracted with anhydrous diethyl ether. The combined extracts were filtered to remove hydrochloride salts and again concentrated *in vacuo* to give chloride (**55**) as a viscous pale yellow oil. This was then redissolved in anhydrous ether (20 cm^3) and the solution cooled to 0 °C. 2, 4, 6-trimethylphenylmagnesium bromide[47] (2 M diethyl ether solution, 2.5 equivalents, 9.7 cm^3, 19.4 mmol) was added dropwise over 10 minutes and the cloudy mixture stirred at 0 °C for 1 hour. It was then warmed to room temperature and stirred for a further 3 hours (or until all chloride was consumed by TLC). The mixture was then

poured into an equal volume of saturated aqueous ammonium chloride solution and extracted with DCM (3 x 7 cm^3). The combined organic extracts were dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on silica eluting with 0→50% v/v ethyl acetate- petrol. This afforded phosphinamide (**52**) as a white solid which was further purified by recrystallisation from toluene (253 mg, 9%). The configuration at phosphorus assigned by comparison with literature data; isolated as a single diastereoisomer[48], $[\alpha]_D^{19}$= -10.8 (*c* 0.01, chloroform) (lit.,[48] -10.5° *c*0.01, chloroform); δ_H (270 MHz, $CDCl_3$) 1.63 (3 H, d, J 6.8, CHC*H*$_3$), 2.27 (3 H, s, 4-Me), 2.35 (6 H, s, 2-Me and 4-Me), 3.16 (1 H, br t, J 9, NH), 4.51 (1 H, m, C*H*CH_3), 6.82 (2 H, d, J 3.7, aryl H), 7.23 (5 H, s, aryl H), 7.4-7.43 (3 H, m, aryl H), 7.64-7.69 (2 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 21.0 (q), 23.7 (q), 25.6 (q), 51.1 (d), 126.1, 127.0, 128.3, 128.4, 128.5, 130.4, 130.6, 130.8, 131.0, 141.3, 143.4 (d, J_{PC} 10), 145.1 (d, J_{PC} 5.5); *m/z* (CI) 364 (M^++1, 100%), 290 (68), 274 (7), 245 (9), 120 (100), 105 (32), 91 (15), 79 (32).

(1R)-N-(1-phenethyl)-P-phenyl-P-(pentafluorophenyl) phosphinamide (60).

This compound was prepared according to the above procedure using chloride (**55**) (2 0 g, 7.16 mmol) and pentafluorophenylmagnesium bromide[47] (2 M diethyl ether solution, 9 cm^3, 18 mmol) in anhydrous diethyl ether (100 cm^3). Phosphonamide (**60**) was obtained as a colourless solid (824 mg, 28%). The compound was isolated as a single diastereoisomer (configuration at phosphorus was not determined), m. p. 208-210 °C (from DCM/ hexane); (found C, 58.0; H, 3.6; N, 3.2. $C_{20}H_{15}F_5NOP$ requires C, 58.39; H, 3.65; N, 3.41%); $[\alpha]_D^{22}$= -20.5 (*c* 0.2, methanol); υ_{max} (nujol)/ cm^{-1} 3262, 1523, 1468, 1377, 1293, 1215, 1120, 1101, 1086, 1018, 976 and 958; δ_H (270 MHz, $CDCl_3$) 1.61 (3 H, d, J 7, CHC*H*$_3$), 3.59 (1 H, br t, J 8, NH), 4.68 (1 H, m, C*H*CH_3), 7.15-7.28 (5 H, m, aryl H), 7.45-7.61 (3 H, m, aryl H), 7.83 (2 H, dd, J 13.7 and 7.1, aryl H); δ_C (68 MHz, $CDCl_3$) 24.8 (dq, J_{PC} 7.7), 51.0 (d), 126.1, 127.5, 128.4, 128.8, 128.9, 130.8, 131.0, 133.0,

133.1, 143.5; δP (162 MHz, $CDCl_3$) 13.8 (1 p, s); *m/z* (CI) 412 (M^++1, 100%), 392 (29), 308 (8), 120 (40).

Section 4.3: Electron Withdrawing Substituents on Nitrogen.

Preparation of R-(+)-N-phenylsulfonyl-α methylbenzylamine.

To a stirred solution of R-(+)-α methylbenzylamine (6 cm^3, 46.5 mmol) and triethylamine (16.2 cm^3, 116.3 mmol) in acetonitrile (30 cm^3) at 0 °C was added benzenesulfonyl chloride (6.5 cm^3, 51.2 mmol) dropwise over 5 minutes. The resulting white slurry was warmed to room temperature and stirred for 2 hours. It was then poured into saturated aqueous ammonium chloride solution (30 cm^3) and extracted with diethyl ether (3 x 10 cm^3). The combined organic extracts were dried (sodium sulfate) and concentrated *in vacuo* to afford the sufonyl amine as a white solid which was purified by recrystallisation from DCM/ hexane to give white needles (10.8 g, 89%), m. p. 95-97 °C (from DCM/ hexane); (found C, 64.1; H, 5.7; N, 5.35. $C_{14}H_{15}NO_2S$ requires C, 64.37; H, 5.75; N, 5.36%); $[\alpha]_D^{19}$= +62.2 (*c* 2.14, chloroform); υ_{max} (nujol)/ cm^{-1} 3241, 1440, 1322, 1161, 1087, 871 and 719; δ_H (270 MHz, $CDCl_3$) 1.43 (3 H, d, J 7, $CHCH_3$), 4.49 (1 H, p, J 7, $CHCH_3$), 5.14 (1 H, br d, J 7, NH), 7.06-7.1 (2 H, m, aryl H), 7.12-7.21 (3 H, m, aryl H), 7.36-7.51 (3 H, m, aryl H), 7.71-7.75 (2 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 23.4 (q), 53.5 (d), 125.9 (d), 126.8 (d), 127.1 (d), 128.2 (d), 128.6 (d), 132.1 (d), 140.5 (s), 141.9 (s); *m/z* (CI) 262 (M^++1, 100%), 246 (22), 184 (26), 158 (10), 120 (20), 105 (37).

Preparation of R-(-)-(N-phenylsulfonyl)(N-1-phenethyl)-diphenylphosphinamide (56).

Sodium hydride (60% suspension in oil, 114 mg, 2.85 mmol) was washed with dry petrol (3 x 1 cm^3) then slurried in anhydrous THF (10 cm^3). R-(+)-N-

phenylsulfonyl-α methylbenzylamine (prepared as described above) (0.5 g, 1.9 mmol) was then added portionwise under a rapid stream of nitrogen. The resulting white slurry was stirred at room temperature for 1 hour. Diphenylphosphinic chloride (0.4 cm^3, 2.09 mmol) was added and the mixture stirred at room temperature for 8 hours. The mixture was then poured into saturated aqueous ammonium chloride solution (5 cm^3) and extracted with ethyl acetate (3 x 5 cm^3). The combined organic extracts were dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on silica eluting with 0→40% v/v ethyl acetate-petrol. This afforded phosphinamide (**56**) as a white solid (328 mg, 38%), m. p. 63-65 °C (from DCM/ hexane); (found C, 67.3; H, 5.42; N, 2.9. $C_{26}H_{24}NO_3S$ requires C, 67.68; H, 5.21; N, 3.04%); $[\alpha]_D^{26}$= -2.2 (*c* 0.74, chloroform); υ_{max} (nujol)/ cm^{-1} 1377, 1214, 1164, 1121, 903, 249, 726 and 690; δ_H (270 MHz, $CDCl_3$) 1.84 (3 H, d, J 7, $CHCH_3$), 5.56 (1 H, dq, J 12.7 and 6.8, $CHCH_3$), 6.89 (2 H, m, aryl H), 7.1-7.27 (5 H, m, aryl H), 7.37-7.59 (9 H, m, aryl H), 7.61-7.89 (4 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 19.2 (q), 58.0 (d), 127.4, 127.6, 127.8, 127.9, 128.0, 128.1, 128.2, 122.4, 128.9, 132.2, 132.5, 132.8, 133.0, 133.2, 138.6 (s), 140.2 (s); δ_P (162 MHz, $CDCl_3$) 32.6 (1 P, s); *m/z* (CI) 462 (M^++1, 5%), 398 (10), 358 (100), 320 (45), 274 (60), 232 (38), 218 (22), 201 (12), 143 (15), 105 (29), 89 (57).

Preparation of Oxzazolidinones.

The preparation of these compounds was based on a literature procedure.[50]

Preparation of 2-Oxazolidinone.

A stirred mixture of ethanolamine (4.9 cm^3, 82 mmol), diethyl carbonate (20 cm^3, 169 mmol) and anhydrous potassium carbonate (1.13 g, 8.2 mmol) was heated to ca. 130 °C and the evolved ethanol removed by distillation. Once

distillation appeared to cease the mixture was cooled to room temperature and diluted with DCM (20 cm^3). The solution was then washed with water (2 x 5 cm^3) then saturated aqueous brine (5 cm^3) and dried (magnesium sulfate). The solvent was then removed *in vacuo* to give 2-oxazolidinone as a white solid which was further purified by recrystallisation from ethyl acetate/ hexane (4.85 g, 68%), m. p. 86-88 °C (lit.,[50] 87-89 °C); δ_H (270 MHz, $CDCl_3$) 3.65 (2 H, t, J 8.8, CH_2), 4.45 (2 H, dd, J 8.5 and 7, CH_2), 6.59 (1 H, br s, NH).

S-4-isopropyl-2-oxazolidinone.

This compound wa prepared according to the above procedure using S-valinol (1.51 g, 15 mmol), diethyl carbonate (3.6 cm^3, 30 mmol) and anhydrous potassium carbonate (200 mg, 1.5 mmol). S-4-isopropyl-2-oxazolidinone was isolated as a white solid which was further purified by recrystallisation from ethyl acetate/ hexane(1.53 g, 79%), m. p. 70-71 °C (lit.,[50] 70-73 °C); $[\alpha]_D^{20}$= -16.5 (*c* 6, ethanol) (lit.,[50] $[\alpha]_D^{20}$= -17 (*c* 6, ethanol)); δ_H (270 MHz, $CDCl_3$) 0.77 (3 H, d, J 6.8, $(CH_3)_2CH$), 0.83 (3 H, d, J 6.6 , $(CH_3)_2CH$), 1.61 (1 H, m, $(CH_3)_2CH$), 3.51 (1 H, m, $CHCH_2$), 3.97 (1 H, dd, J 9.8 and 6.2, $CHCH_2$), 4.31 (1 H, t, J 8.6, $CHCH_2$), 7.11 (1 H, br s, NH).

Preparation of N-diphenylphosphinyl Oxazolidinones.

General Procedure from Oxazolidinones:

The following procedure is typical.

Preparation of N-diphenylphosphinyl-2-oxazolidinone (57).

Sodium hydride (60% suspension in oil, 0.5 g, 12.6 mmol) was washed with dry petrol (3 x 5 cm^3) then slurried in anhydrous THF (20 cm^3). 2-Oxazolidinone

(1.0 g, 11.5 mmol) was the added portionwise under a rapid stream of nitrogen. The resulting mixture was then stirred for 1 hour at room temperature. Diphenylphosphinic chloride (2.2 cm^3, 11.5 mmol) was added dropwise and the mixture stirred at room temperature for 6 hours (or until all of the oxazolidinone was consumed by TLC). The mixture was then poured into saturated aqueous ammonium chloride solution (10 cm^3) and extracted with ethyl acetate (3 x 10 cm^3). The combined organic extracts were dried (magnesium sulfate) and concentrated *in vacuo* to give phosphinamide (**57**) as a white solid which was further purified by recrystallisation from DCM/ hexane. Obtained as white needles (2.41 g, 73%), m. p. 118-121 °C (from DCM/ hexane); (found C, 62.8; H, 4.95; N, 4.9. $C_{15}H_{14}NO_3P$ requires C, 62.72; H, 4.88; N, 4.88%); υ_{max} (nujol)/ cm^{-1} 1750, 1213, 1121, 1052, 768, 727 and 692; δ_H (400 MHz, $CDCl_3$) 3.93 (2 H, t, J 7.6, C*H*$_2$), 4.38 (2 H, t, J 7.6, C*H*$_2$), 7.42-7.46 (4 H, m, aryl H), 7.49-7.56 (2 H, m, aryl H), 7.79-7.84 (4 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) 43.8 (t), 63.9 (dt, J_{PC} 7.3), 128.5 (dd, J_{PC} 12.8), 131.8 (dd, J_{PC} 11), 132.9 (dd, J_{PC} 3.6), 156.2 (d, J_{PC} 7.4); δ_P (162 MHz, $CDCl_3$) 26.5 (1 P, s); *m/z* (CI) 288 (M^++1, 100%), 243 (12), 201 (7), 88(25).

N-diphenylphosphinyl-(S)-4-Isopropyl-2-oxazolidinone (58).

This compound was prepared according to the above general procedure using sodium hydride (60% suspension in oil, 340 mg, 8.53 mmol), S-4-isopropyl-2-oxazolidinone (1.0 g, 7.75 mmol) and diphenylphosphinic chloride (1.48 cm^3, 7.75 mmol) in anhydrous THF (20 cm^3). Phosphinamide (**58**) was obtained as a white solid which was further purified by recrystallisation from DCM/ hexane. Obtained as white needles (2.18 g, 85%), m. p. 147-149 °C (from DCM/ hexane); (found C, 65.3; H, 6.1; N, 3.9. $C_{18}H_{20}NO_3P$ requires C, 65.65; H, 6.08; N, 4.26%); $[\alpha]_D^{26}$= +120.2 (*c* 1.58, chloroform); υ_{max} (nujol)/ cm^{-1} 1747, 1439, 1393, 1327, 1205, 1126, 1052, 971, 752, 726 and 698; δ_H (270 MHz, $CDCl_3$) 0.68 (3 H, d, J 7,

(CH_3)$_2$CH), 0.8 (3 H, d, J 7, (CH_3)$_2$CH), 2.21 (1 H, m, (CH_3)$_2$C*H*), 4,19 (1 H, dd, J 7.3 and 3, C*H*CH$_2$), 4.34 (1 H, t, J 8.6, CHC*H*$_2$), 4.44-4.47 (1 H, m, CHC*H*$_2$), 7.25-7.81 (8 H, m, aryl H), 8.04 (2 H, dd, J 13.2 and 7.4, aryl H); δ_C (68 MHz, $CDCl_3$) 14.2 (q), 17.8 (q), 30.8 (d), 60.6 (dd, J_{PC} 3.3), 65.0 (dt, J_{PC} 7.7), 128.2 (dd, J_{PC} 2.2), 128.4, 131.2 (dd, J_{PC} 7.7), 131.4 (dd, J_{PC} 11), 132.0 (dd, J_{PC} 11), 132.6, 132.8 (dd, J_{PC} 2.2), 156.6 (d, J_{PC} 7.7), 203.6 (s); δ_P (162 MHz, $CDCl_3$) 27.0 (1 P, s); *m/z* (CI) 330 (M^++1, 100%), 286 (10), 201 (15), 158 (32), 130 (36).

Section 4.4: Conformationally Restricted Systems.

Preparation of N, N'-bis (1-(R)-phenylethyl)-1, 2-ethylenediamide .

To a stirred solution of R-(+)-α methylbenzylamine (2 cm^3, 15.5 mmol) and triethylamine (6.5 cm^3, 46.5 mmol) in DCM (40 cm^3) at 0 °C was added oxalyl chloride (0.7 cm^3, 7.8 mmol) dropwise over 5 minutes. The resulting thick white slurry was warmed to room temperature and stirred for 3 hours. Saturated aqueous ammonium chloride solution (20 cm^3) was then added and the mixture extracted with DCM (3 x 10 cm^3). The combined organic extracts were dried (sodium sulfate) and concentrated *in vacuo* to give the *bis*-amide as a pale yellow solid which was further purified by recrystallisation from DCM/ hexane to give white needles (1.95 g, 84%), m. p. 195-199 °C (from DCM/ hexane); $[\alpha]_D^{19}$= +97.1 (*c* 0.42, chloroform); υ_{max} (nujol)/ cm^{-1} 3301, 1650, 1511, 1224 and 1126; δ_H (270 MHz, $CDCl_3$) 1.54 (6 H, d, J 7, CHC*H*$_3$), 5.06 (2 H, dq, J 7.6 and 7.5, C*H*CH$_3$), 7.23-7.36 (10 H, m, aryl H), 7.71 (2 H, br d, J 7.5, NH); δ_C (68 MHz, $CDCl_3$) 21.7 (q), 49.5 (d), 126.2 (d), 127.7 (d), 128.8 (d), 141.95 (s), 158.9 (s); *m/z* (CI) 297 (M^++1, 13%), 193 (54), 145 (6), 105 (100); (found $[M+H]^+$, 297.1603. $C_{18}H_{21}N_2O_2$ requires *m/z*, 297.1602).

Preparation of N, N'-bis (1-(R)-phenylethyl)-1, 2-ethylenediamine (63).

To a refluxing solution of N, N'-*bis* (1-(R)-phenylethyl)-1, 2-ethylenediamide (1.51 g, 5.1 mmol) in anhydrous THF (50 cm^3) was added lithium aluminium hydride (4 equivalents, 0.77 g, 20.4 mmol) portionwise [CARE!: vigorous effervescence]. The stirred mixture was heated at reflux for 48 hours. It was then cooled to room temperature and water (1 cm^3) was then added dropwise followed by 15% w/v aqueous sodium hydroxide solution (5 cm^3). The resulting mixture was stirred at room temperature for 1 hour. It was then filtered through celite and the residues washed with DCM (3 x 50 cm^3). The filtrate was dried (magnesium sulfate) and concentrated *in vacuo*. The residue was a brown oil which was further purified by distillation under reduced pressure b. p. 145-148 °C, 0.5 mmHg (lit.,[61] 110 °C, 0.02 mmHg). The product was a colourless oil (1.31 g, 95%), $[\alpha]_D^{26}$= +69.9 (*c* 1, chloroform) (lit.,[61] ent- $[\alpha]_D^{20}$= -69.4 (*c* 1.1, chloroform); δ_H (270 MHz, $CDCl_3$) 1.35 (6 H, d, J 6.6, CHC*H*$_3$), 2.53 (4 H, s, C*H*$_2$), 3.4 (2 H, br s, NH), 3.65 (2 H, q, J 6.8 C*H*CH$_3$), 7.2-7.41 (10 H, m, aryl H).

Preparation of N, N'-dibenzyl-1, 3-propanediamine.

To a stirred solution of 1, 3-diaminopropane (5 cm^3, 59.9 mmol) and triethylamine (20.8 cm^3, 149.7 mmol) in DCM (160 cm^3) at 0 °C was added benzoyl chloride (13.9 cm^3, 119.8 mmol) dropwise over 10 minutes. This resulted in the formation of a heavy white precipitate. The mixture was then allowed to warm to room temperature. It was then quenched by addition of saturated aqueous ammonium chloride solution (60 cm^3) and extracted with DCM (3 x 50 cm^3). The combined organic extracts were then washed with saturated aqueous brine (30 cm^3), dried (sodium sulfate) and concentrated *in vacuo* to give a white solid. The crude *bis*-amide was redissolved in anhydrous THF (300 cm^3) and heated to reflux.

Lithium aluminium hydride (5.36 g, 141.8 mmol) was then added portionwise [CARE!: vigorous effervescence] and the mixture heated at reflux for 36 hours. It was then cooled to room temperature and water (10 cm^3) was then added dropwise with external cooling. 15% w/v aqueous sodium hydroxide solution (6 cm^3) was then added dropwise followed by a further 15 cm^3 of water. The resulting mixture was stirred at room temperature for 2 hours. It was then filtered through celite and the residue washed with diethyl ether (3 x 75 cm^3). The organic phase of the filtrate was separated, dried (magnesium sulfate) and concentrated *in vacuo* to give the diamine as a yellow oil which was further purified by distillation under reduced pressure b. p. 187-188 ^oC, 0.5 mmHg (lit.,[115] 189 ^oC, 0.6 mmHg). The product was a colourless oil (10.35 g, 68%), δ_H (270 MHz, $CDCl_3$) 1.43 (2 H, br s, NH), 1.68 (2 H, p, J 6.8, 2-CH_2), 2.69 (4 H, t, J 6.8, 1- and 3-CH_2), 3.76 (4 H, s, CH_2Ph), 7.29 (10 H, m, aryl H).

Preparation of *C2* Symmetric Cyclic Phosphonamides.

General Procedure:

The following procedure is typical.

Preparation of 1,3-bis (1-(R)-phenylethyl)-2-ethyl-1, 3, 2-diazaphospholidine 2-oxide (61).

To a stirred solution of N, N'-*bis* (1-(R)-phenylethyl)-1, 2-ethylenediamine (0.52 g, 1.92 mmol) and triethylamine (0.53 cm^3, 3.84 mmol) in DCM (20 cm^3) at 0 ^oC was added ethylphosphonic dichloride (0.21 cm^3, 1.92 mmol) dropwise. The resulting mixture was warmed to room temperature and stirred for 18 hours. It was then poured into an equal volume of saturated aqueous ammonium chloride solution and extracted with DCM (3 x 10 cm^3). The combined organic extracts were dried (sodium sulfate) and concentrated *in vacuo*. The residue was purified on silica

eluting with 0→10% v/v methanol- DCM. This afforded phosphonamide (**61**) as a colourless oil in (328 mg, 50%), $[\alpha]_D^{19}$= +31.8 (*c* 0.11, chloroform); υ_{max} (film)/ cm^{-1} 3059, 2973, 2875, 1378, 1278 and 1209; δ_H (270 MHz, $CDCl_3$) 1.05 (3 H, dt, J 19.8 and 7.7, CH_2CH_3), 1.61 (3 H, d, J 6.8, $CHCH_3$), 1.63 (3 H, d, J 7, $CHCH_3$), 1.94 (2 H, dq, J 16.1 and 7.7, CH_2CH_3), 2.76-2.93 (3 H, m, CH_2), 3.01-3.1 (1 H, m, CH_2), 4.42-4.62 (2 H, m, $CHCH_3$), 7.24-7.48 (10 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 7.8 (dq, J_{PC} 5.5), 19.2 (q), 20.1 (q), 23.1 (dt, J_{PC} 119.9), 41.9 (t), 42.0 (t), 53.0 (dd, J_{PC} 6.6), 53.8 (dd, J_{PC} 5.5), 128.6 (d), 127.1 (d), 127.15 (d), 127.3 (d), 128.3 (d), 128.4 (d), 142.1 (d J_{PC} 4.3), 143.0 (d, J_{PC} 4.3); δ_P (162 MHz, $CDCl_3$) 40.8 (1 P, s); *m/z* (EI) 342 (M^+, 18%), 327 (90), 313 (21), 265 (10), 237 (13), 223 (25), 105 (100); (found $[M]^+$, 342.1853. $C_{20}H_{27}N_2OP$ requires *m/z*, 342.1861).

1, 3-dibenzyl-2-ethyl-1, 3, 2-diazaphosphorinane 2-oxide (62)

This compound was prepared according to the above general procedure using N, N'-dibenzyl-1, 3-propanediamine (1.5 g, 5.9 mmol), triethylamine (1.64 cm^3, 11.8 mmol) and ethylphosphonic dichloride (0.63 cm^3, 5.9 mmol) in DCM (50 cm^3). Phosphonamide (**62**) was isolated as a white solid (1.31 g, 68%), m. p. 79-82 °C (from DCM/ hexane); (found C, 69.4; H, 7.7; N, 8.5. $C_{19}H_{25}N_2OP$ requires C, 69.51; H, 7.62; N, 8.54%); υ_{max} (nujol)/ cm^{-1} 1378, 1285, 1202, 1049, 920 and 721; δ_H (270 MHz, $CDCl_3$) 1.19 (3 H, dt, J 18.5 and 7.7, CH_2CH_3), 1.53-1.61 (1 H, m, 5-CH_2), 1.71-1.85 (1 H, m, 5-CH_2), 1.93 (2 H, dq, J 14.6 and 7.5, CH_2CH_3), 2.93-3.02 (4 H, m, 4- and 6-CH_2), 4.09 (2 H, dd, J 14.9 and 7, CH_2Ph), 4.35 (2 H, dd, J 14.9 and 6.4, CH_2Ph), 7.23-7.41 (10 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) 7.3 (dq J_{PC} 5.5), 19.2 (dt, J_{PC} 115.2), 24.7 (t), 46.3 (t), 50.4 (t), 126.7 (d), 127.5 (d), 127.8 (d), 127.9 (d), 128.6 (d), 128.7 (d), 138.4 (d, J_{PC} 5.5);δ_P (162 MHz, $CDCl_3$) 34.1 (1 P, s); *m/z* (EI) 328 (M^+, 100%), 299 (14), 148 (35), 91 (14).

R, R-(+)-4, 5-tetramethylene-2-phenyl-1, 3, 2-diazaphosphorine 2-oxide (64).

This compound was prepared according to the above general method using R, R-(-)-diaminocyclohexane (400 mg, 3.51 mmol), triethylamine (0.98 cm^3, 7.02 mmol) and phenylphosphonic dichloride (0.51 cm^3, 3.51 mmol) in DCM (10 cm^3). Phosphonamide (**64**) was isolated as a white solid (696 mg, 84%), m. p. 186-188 °C (d) (from DCM/ petrol); (found C, 60.6; H, 7.4; N, 11.6. $C_{12}H_{17}N_2OP$ requires C, 61.02; H, 7.20; N, 11.86%); $[\alpha]_D^{12}$ = +4.3 (*c* 0.51, methanol); υ_{max} (nujol)/ cm^{-1} 3215, 1312, 1201, 1183, 1108, 1075, 951, 897 and 744; δ_H (270 MHz, $CDCl_3$) 1.21-1.52 (4 H, m, C*H*$_2$), 1.64-1.98 (4 H, m, C*H*$_2$), 2.77-3.04 (3H, m, C*H* and 2 x NH), 3.22 (1 H, m, C*H*), 7.31-7.49 (3 H, m, aryl H), 7.83 (2 H, m, aryl H); δ_C (68 MHz, CD_3OD) 26.2 (t), 26.8 (dt, J_{PC} 4.4), 34.8 (t), 36.2 (t), 57.1 (dd, J_{PC} 5.5), 59.1 (dd, J_{PC} 18), 129.8, 129.9, 130.0, 130.1, 132.6, 132.8, 132.9, 133.6; δ_P (162 MHz, $CDCl_3$) 25.8 (1 P, s); *m/z* (EI) 236 (M^+, 100%), 194 (7), 101 (77), 86 (47); (found $[M]^+$, 236.1037. $C_{12}H_{17}N_2OP$ requires *m/z*, 236.1078).

Preparation of Sp, R-(-)-dihydrobenzaphosphole oxide (25).

This compound was obtained by desilylation of a sample of the corresponding *t*-BDPS protected phosphinamide prepared in the Wills group. The synthesis and X-ray structure of this precursor has been reported.[53] The deprotection was affected as follows:

To a stirred solution of Sp , R-(-)-N-(*t*-butyldiphenylsilyl) dihydrobenzaphosphole oxide (1.0 g, 2.07 mmol) in THF (17 cm^3) was added TBAF (1 M THF solution, 4.1 cm^3, 4.15 mmol) dropwise. The resulting solution was stirred at room temperature for 3 hours. It was then poured into saturated aqueous ammonium chloride solution (10 cm^3) and extracted with ethyl acetate (3 x 5 cm^3). The combined organic extracts were dried (sodium sulfate) and

concentrated *in vacuo*. The residue was purified on silica eluting with 0→70% v/v ethyl acetate- petrol. This afforded phosphinamide (**25**) as a white solid (457 mg, 91%), m. p. 232-234 °C (d) (from DCM/ hexane); (found C, 69.0; H, 5.8; N, 5.6. $C_{14}H_{14}NOP$ requires C, 69.13; H,5.80; N, 5.76%); $[\alpha]_D^{20}$= -131.2 (*c* 0.87, methanol); υ_{max} (nujol)/ cm^{-1}3195, 2971, 1446, 1209, 1182, 1115, 754, 730 and 694; δ_H (400 MHz, $CDCl_3$) 1.64 (3 H, d, J 6.4, CHC*H*$_3$), 3.71 (1 H, br d, J 11.6, NH), 4.82 (1 H, m, C*H*CH_3), 7.37-7.41 (4 H, m, aryl H), 7.42-7.49 (1 H, m, aryl H), 7.52-7.64 (2 H, m, aryl H), 7.67-7.72 (2 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) 25.7 (q), 56.1 (dd, J_{PC} 7.3), 123.9, 124.0, 128.6, 128.8, 128.9, 130.4 (s), 132.2 (dd, J_{PC} 23.8), 132.6 (dd, J_{PC} 11.4), 134.0 (s), 149.0 (d, J_{PC} 20.1); δ_P (162 MHz, $CDCl_3$) 34.0 (1 P, s); *m/z* (CI) 244 (M^+, 100%), 228 (20).

Section 4.5: Combined Donor Catalysts.

Preparation of Chiral N-methyl Diamines.

The N-methyl diamines required for the preparation of the triamide catalysts were prepared according to a literature procedure.[59,65]

Preparation of R, R-(-)-N, N'-Dimethylcyclohexane-1, 2-diamine (73).

To a solution of R, R-(-)-cyclohexane-1, 2-diamine (4.5 g, 39.5 mmol) in toluene (60 cm^3) at 0 °C was added ethyl choroformate (8.95 cm^3, 93.6 mmol) and a solution of sodium hydroxide (3.74 g, 93.6 mmol) in water (4 cm^3) simultaneously with rapid stirring at such a rate as to maintain the reaction temperature between 0 and 10 °C. Once addition was complete the thick white slurry was warmed to room temperature and stirred for 3 hours. The heavy precipitate was then filtered off and washed with DCM (3 x 30 cm^3). The combined organic extracts were then dried (magnesium sulfate) and concentrated *in vacuo*. The residue was then recrystallised from DCM/ pentane to afford the dicarbamate as white needles (9.83 g, 97%).

To a solution of lithium aluminium hydride (1.76 g, 46.4 mmol) in anhydrous THF (80 cm^3) was slowly added the dicarbamate (3.0 g, 11.6 mmol) portionwise at room temperature with rapid stirring. Once addition was complete the mixture was heated at reflux for 24 hours [CARE!: reflux temperature must be approached gradually to prevent a vigorous exothermic reaction]. The mixture was then cooled and ethylenediamine (4.25 cm^3) added slowly followed by a 15% w/v aqueous sodium hydroxide solution (2 cm^3) and water (4 cm^3). It was then stirred for 30 minutes at room temperature. The precipitate was removed by filtration through celite and the residues washed with diethyl ether (3 x 30 cm^3). The filtrate was then concentrated *in vacuo*. The resulting oil was redissolved in diethyl ether

(30 cm^3) and the aqueous phase removed. The solution was dried (sodium sulfate) and again filtered through celite. The filtrate was then concentrated *in vacuo* to give diamine (**73**) as an oil which was purified by distillation under reduced pressure (1.36 g, 83%), b. p. 76-80 °C (15 mmHg) (lit.,[59] 78-80 °C (18 mmHg)); $[\alpha]_D^{24}$= -115.4 (*c* 4.36, chloroform) (lit.,[59] $[\alpha]_D^{20}$= -145.7 (*c* 4.47, chloroform)); δ_H (270 MHz, $CDCl_3$) 0.93-1.14 (4 H, m, C*H*$_2$), 1.18-2.09 (8 H, m, C*H* , C*H*$_2$ and NH), 2.35 (6 H, s, NMe).

S, S-(-)-N, N'-Dimethyl-1, 2-diphenylethylene-1, 2-diamine.

This compound was prepared according to the above method. The dicarbamate was prepared using S, S-(-)-1, 2-diphenyl-1, 2-ethylenediamine (1.0 g, 4.72 mmol), ethyl chloroformate (1.1 cm^3, 11.3 mmol) and aqueous sodium hydroxide solution (0.45 g sodium hydroxide in 0.5 cm^3 water) in toluene (15 cm^3) and was obtained as a white solid (1.53 g, 91%). Reduction of this compound (0.75 g, 2.11 mmol) using lithium aluminium hydride (0.32 g, 8.44 mmol) in THF (20 cm^3) afforded the N, N'-dimethyl amine as a white solid (442 mg, 81%), m. p. 43-45 °C (from toluene) (lit.,[65] 46-47 °C); $[\alpha]_D^{20}$= -22.5 (*c* 0.26, chloroform) (lit.,[65] $[\alpha]_D^{25}$= -18.02 (*c* 1, chloroform)); δ_H (270 MHz, $CDCl_3$) 1.95 (2 H, br s, NH), 2.34 (6 H, s, NMe), 3.63 (2 H, s, C*H*$_2$Ph), 7.1-7.47 (10 H, m, aryl H).

Preparation of Phosphoramidic Chlorides.

General Procedure:

These compounds were prepared *via* a modified literature procedure.[59] The following procedure is typical.

Preparation of 2-chloro-1, 3-dimethyl-1, 3, 2-diazaphospholidine-2-oxide (68, R=Me).

To a stirred solution of N, N'-dimethylethylenediamine (**67**, R^1=Me) (0.39 cm^3, 3.7 mmol) and triethylamine (1.3 cm^3, 9.3 mmol) in DCM (30 cm^3) at 0 °C was added phosphorus oxychloride (0.35 cm^3, 3.7 mmol) dropwise over 5 minutes. The resulting solution was then warmed to room temperature and stirred for 12 hours. It was then concentrated *in vacuo* and the residue purified on silica eluting with 0→30% v/v ethyl acetate- petrol. This afforded chloride (**68**, R^1=Me) as a white solid which was further purified by recrystallisation from toluene (598 mg, 95%), m. p. 169-171 °C (from toluene); υ_{max} (nujol)/ cm^{-1} 3024, 2982, 1454, 1992, 1265, 1117 and 765; δ_H (270 MHz, $CDCl_3$) 2.61 (6 H, d, J 12.8, NMe), 2.91-3.04 (2 H, m, C*H*$_2$), 3.17-3.28 (2 H, m, C*H*$_2$); δ_C (100 MHz, $CDCl_3$) 31.3 (q), 45.6 (t), 45.7 (t); δ_P (162 MHz, $CDCl_3$) 28.9 (1 P, s); *m/z* (EI) 170 (M^+, 30%), 168 (M^+, 100%), 133 (60), 86 (50), 43 (100); (found $[M]^+$, 168.0198. $C_4H_{10}N_2POCl^{35}$ requires *m/z*, 168.0219).

2-chloro-1, 3-((R)-1-phenylethyl)-1, 3, 2-diazaphospholidine-2-oxide (68, R=(R)-1-phenylethyl).

This compound was prepared according to the above general procedure using N, N'-*bis* (1-(R)-phenylethyl)-1, 2-ethylenediamine.(**63**). The chloride (**68**, R= (R)-1-phenylethyl) was obtained as white needles (780 mg, 60%), m. p. 96-98 °C (from DCM, hexane); (found C, 61.7; H, 6.4; N, 8.0. $C_{18}H_{22}N_2OPCl$ requires C, 61.98; H, 6.36; N, 8.03%); $[\alpha]_D^{22}$= +8.7 (*c* 0.54, chloroform); υ_{max} (nujol)/ cm^{-1} 3027, 2981, 1492, 1454, 1394, 1266, 1226, 1180, 1117, 1082, 973 and 765; δ_H (270 MHz, $CDCl_3$) 1.61 (3 H, d, J 6.95, CHC*H*$_3$), 1.66 (3 H, d, J 6.8, CHC*H*$_3$), 2.65-2.93 (4 H, m, C*H*$_2$), 4.17 (1 H, dq, J 7.5 and 6.8, C*H*CH$_3$), 4.69 (1 H, dq, J 10.5 and 7, C*H*CH$_3$), 7.19-7.38 (10 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) 17.0 (dq, J_{PC} 7.3),

21.2 (dq, J_{PC} 9.2), 38.2 (dt, J_{PC} 14.6), 42.4 (dt, J_{PC} 14.7), 52.2 (dd, J_{PC} 7.3), 56.6 (dd, J_{PC} 7.3), 126.9 (d), 127.3 (d), 127.6 (d), 127.7 (d), 128.5 (d), 128.7 (d), 140.5 (d, J_{PC} 5.5), 141.8 (d, J_{PC} 10.9); δ_P (162 MHz, $CDCl_3$) 24.2 (1 P, s); *m/z* (CI) 351 (M^+, 30%), 349 (M^+, 100%), 333 (25), 313 (19), 105 (20).

Phosphoramidic Chloride (74).

This compound was prepared according to the above general procedure using R, R-(-)-N, N'-dimethylcyclohexane-1, 2-diamine (**73**) (1.36 g, 9.58 mmol), triethylamine (3.3 cm^3, 23.95 mmol) and phosphorus oxychloride (0.9 cm^3, 9.58 mmol) in DCM (50 cm^3). Chloride (**74**) was obtained as white needles (1.92 g, 90%), m. p. 68-69 °C (from DCM/ hexane) (lit.,[59] 70 °C); $[\alpha]_D^{21}$= -55.4 (*c* 5.5, DCM) (lit.,[59] $[\alpha]_D^{20}$= -57.5 (*c* 5.7, DCM)); δ_H (270 MHz, $CDCl_3$) 1.09-1.32 (4 H, m, C*H*$_2$), 1.79-1.96 (4 H, m, C*H*$_2$), 2.45-2.52 (4 H, m, C*H* and NMe), 2.59 (3 H, d, J 11.9, NMe), 2.78 (1 H, m, C*H*).

Phosphoramidic Chloride (87).

This compound was prepared according to the above general procedure using S, S-(-)-N, N'-Dimethyl-1, 2-diphenylethylene-1, 2-diamine (200 mg, 0.83 mmol), triethylamine (0.29 cm^3, 2.08 mmol) and phosphorus oxychloride (0.08 cm^3, 0.83 mmol) in DCM (10 cm^3). Chloride (**87**) was obtained as a colourless oil (149 mg, 56%), $[\alpha]_D^{22}$= -12.9 (*c* 0.88, chloroform); δ_H (270 MHz, $CDCl_3$) 2.42 (3 H, d, J 14.5, NMe), 2.61 (3 H, d, J 10.4, NMe), 3.84 (1 H, d, J 8.6, C*H*Ph), 4.15 (1 H, dd, J 8.7 and 4.2, C*H*Ph), 7.2-7.39 (10 H, m, aryl H).

Preparation of Triamide Catalysts by Reaction of a Lithiated Amine with a Phosphoramidic Chloride.

General Procedure:

The following procedure is typical.

Preparation of phosphoramide (69).

To a stirred solution of the R-(+)-α methylbenzylamine (1.2 cm^3, 8.9 mmol) in anhydrous THF (15 cm^3) at 0 °C was added *n*-butyllithium (2.5 M hexane solution, 3.6 cm^3, 8.9 mmol) dropwise. The solution was then stirred for 20 minutes at 0 °C, warmed to room temperature and stirred for a further 10 minutes. It was then again cooled to 0 °C and a solution of 2-chloro-1, 3-dimethyl-1, 3, 2-diazaphospholidine-2-oxide (**68**, R^1=Me) (1.5 g, 8.9 mmol) in anhydrous THF (15 cm^3) was added dropwise. The mixture was allowed to warm slowly to room temperature and stirred for 12 hours. It was then poured into saturated aqueous ammonium chloride solution (10 cm^3) and extracted with ethyl acetate (3 x 7 cm^3). The combined organic extracts were dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on silica eluting with 0→10% v/v methanol-DCM. This afforded phosphoramide (**69**) as a white solid (1.53 g, 68%), m. p. 106-108 °C (from DCM/ hexane); $[\alpha]_D^{22}$= +48.6 (*c* 0.92, chloroform); υ_{max} (nujol)/ cm^{-1} 3200, 1951, 1679, 1454, 1378, 1274 and 1000; δ_H (270 MHz, $CDCl_3$) 1.63 (3 H, d, J 6.8, CHC*H*$_3$), 2.35 (3 H, d, J 9.5, NMe), 2.86 (3 H, d, J 9.7, NMe), 3.07-3.57 (5 H, br m, C*H*$_2$ and NH), 4.23 (1 H, m, C*H*CH$_3$), 7.41-7.53 (5 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 25.8 (dq, J_{PC} 7.7), 30.7 (q), 31.2 (dq, J_{PC} 4.4), 46.4 (dt, J_{PC} 13.2), 47.1 (dt, J_{PC} 12.1), 51.2 (d), 125.7 (d), 126.7 (d), 128.3 (d), 146.1 (d, J_{PC} 3.3); δ_P (162 MHz, $CDCl_3$) 24.6 (1 P, s); *m/z* (EI) 253 (M^+, 82%), 120 (100), 42 (9); (found $[M+H]^+$, 254.1421. $C_{12}H_{21}N_3OP$ requires *m/z*, 254.1422).

Phosphoramide (70).

This compound was prepared according to the above general procedure using R-(+)-α methylbenzylamine (0.04 cm^3, 0.29 mmol), *n*-butyllithium (2.5 M hexane solution, 0.12 cm^3, 0.29 mmol) and chloride (**68**, R^1= (R)-1-phenylethyl) (100 mg, 0.29 mmol) in anhydrous THF 2 cm^3. Phosphoramide (**70**) was obtained as a viscous pale yellow oil (49 mg, 39%), $[\alpha]_D^{22}$= +22.5 (*c* 0.18, chloroform); υ_{max} (film)/ cm^{-1} 3217, 1456, 1375, 1170, 978, 744 and 699; δ_H (270 MHz, $CDCl_3$) 1.49 (3 H, d, J 7, CHC*H*$_3$), 1.52 (3 H, d, J 8.2, CHC*H*$_3$), 1.58 (3 H, d, J 7, CHC*H*$_3$), 2.65-2.87 (4 H, m, C*H*$_2$), 3.17 (1 H, br t, J 9.6, NH), 3.59 (1 H, m, C*H*CH$_3$), 4.41-4.52 (2 H, m, C*H*CH$_3$), 7.01-7.51 (15 H, m, aryl H); δ_P (162 MHz, $CDCl_3$) 20.1 (1 P, s); *m/z* (CI) 434 (M^++1, 100%), 419 (31), 329 (45), 106 (100); (found $[M+H]^+$, 434.2360. $C_{26}H_{33}N_3OP$ requires *m/z*, 434.2361).

Phosphoramide (72).

(R, R, R-diastereoisomer). This compound was prepared according to the above general procedure using R-(+)-α methylbenzylamine (0.07 cm^3, 0.54 mmol), *n*-butyllithium (1.43 M hexane solution, 0.32 cm^3, 0.45 mmol) and chloride (**74**) (100 mg, 0.45 mmol) in anhydrous THF (2 cm^3). Phosphoramide (**72**) was obtained as a white solid (61 mg, 44%), m. p. 138-142 °C (from DCM/ hexane); $[\alpha]_D^{22}$= -11.0 (*c* 0.72, chloroform); υ_{max} (nujol)/ cm^{-1} 3239, 2993, 2958, 1641, 1451, 1296, 1193, 1132, 1092, 1040, 978, 950, 899, 761 and 702; δ_H (270 MHz, $CDCl_3$) 1.19-1.31 (4 H, m, C*H*$_2$), 1.42 (3 H, d, J 6.8, CHC*H*$_3$), 1.81-1.95 (4 H, m, C*H*$_2$), 2.13 (3 H, d, J 10.4, NMe), 2.39 (1 H, m, C*H*), 2.53 (3 H, d, J 11.5, NMe), 2.56-2.66 (1 H, m, C*H*), 3.01 (1 H, br m, NH), 4.16 (1 H, m, C*H*CH$_3$), 7.28-7.34 (5 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) 24.3 (t), 25.8 (q), 26.3 (q), 27.9 (q), 28.5 (dt, J_{PC} 8), 51.3 (d), 63.1 (dd, J_{PC} 8.8), 62.8 (dd, J_{PC} 8.8), 125.8 (d), 126.9 (d), 128.5 (d), 146.1 (s); δ_P (162 MHz, $CDCl_3$) 27.3 (1 P, s); *m/z* (CI) 308 (M^++1, 100%), 292

(10), 233 (7), 120 (21); (found $[M+H]^+$, 308.1883. $C_{16}H_{27}N_3OP$ requires *m/z*, 308.1892).

Phosphoramide (75).

(R, R, S-diastereoisomer). This compound was prepared according to the above general procedure using S-(-)-α methylbenzylamine (0.07 cm^3, 0.54 mmol), *n*-butyllithium (1.43 M hexane solution, 0.32 cm^3, 0.45 mmol) and chloride (**74**) (100 mg, 0.45 mmol) in anhydrous THF (2 cm^3). Phosphoramide (**75**) was obtained as a white solid (50 mg, 36%), m. p. 144-145 °C (from DCM/ hexane); $[\alpha]_D^{26}$= -143.5 (*c* 0.37, chloroform); υ_{max} (nujol)/ cm^{-1} 3239, 2993, 2956, 1450, 1297, 1192, 1132, 1072, 1040, 978 and 701;δ_H (270 MHz, $CDCl_3$) 1.17-1.27 (4 H, m, C*H*$_2$), 1.41 (3 H, d, J 6.6, CHC*H*$_3$), 1.64-1.79 (3 H, m, C*H*$_2$), 1.97 (1 H, m, C*H*$_2$), 2.06 (3 H, d, J 11.4, NMe), 2.54-2.56 (5 H, d overlapping m, J 10.6, NMe and C*H*), 3.08 (1 H, br m, NH), 4.02-4.08 (1 H, m, C*H*CH$_3$), 7.21-7.27 (5 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 24.2 (t), 26.2 (q), 27.8 (q), 28.2 (dt, J_{PC} 8.8), 28.3 (q), 51.0 (d), 64.0 (dd, J_{PC} 8.7), 65.1 (dd, J_{PC} 9.9), 126.0 (d), 128.2 (d), 128.4 (d), 146.1 (s); δ_P (162 MHz, $CDCl_3$) 28.1 (1 P, s); *m/z* (EI) 307 (M^+, 5%), 232 (50), 204 (40), 189 (23), 120 (30), 42 (50); (found $[M+H]^+$, 308.1883. $C_{16}H_{27}N_3OP$ requires *m/z*, 308.1892).

Phosphoramide (76).

This compound was prepared according to the above general procedure using benzylamine (0.06 cm^3, 0.54 mmol), *n*-butyllithium (1.56 M hexane solution, 0.29 cm^3, 0.45 mmol) and chloride (**74**) (100 mg, 0.45 mmol) in anhydrous THF (2 cm^3). Phosphoramide (**76**) was obtained as a viscous oil (72 mg, 55%), $[\alpha]_D^{19}$= -61.4 (*c* 0.96, chloroform); υ_{max} (film)/ cm^{-1} 3229, 2933, 2858, 1602, 1449, 1372, 1296, 1194, 1132, 1073, 977, 899, 759 and 702; δ_H (270 MHz, $CDCl_3$) 1.11-1.25

(4 H, m, C*H*$_2$), 1.75 (2 H, m, C*H*$_2$), 1.95 (2 H, m, C*H*$_2$), 2.45 (3 H, d, J 8.2, NMe), 2.48 (3 H, d, J 7.7, NMe), 2.55-2.72 (2 H, m, C*H*), 3.21 (1 H, br s, NH), 3.98 (2 H, br d, J 7, C*H*$_2$Ph), 7.22-7.31 (5 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) 24.2 (t), 28.2 (q), 28.3 (q), 28.4 (t), 44.9 (t), 63.0 (dd, J_{PC} 9.1), 64.6 (dd, J_{PC} 9.1), 127.0 (d), 127.1 (d), 128.4 (d), 140.3 (dd, J_{PC} 5.5); δ_P (162 MHz, $CDCl_3$) 28.9 (1 P, s); *m/z* (EI) 293 (M^+, 100%), 188 (5), 106 (19); (found $[M+H]^+$, 294.1725. $C_{15}H_{25}N_3OP$ requires *m/z*, 294.1735).

Phosphoramide (85).

This compound was prepared according to the above general procedure using R-(+)-α methylbenzylamine (0.07 cm^3, 0.53 mmol), *n*-butyllithium (2.48 M hexane solution, 0.18 cm^3, 0.44 mmol) and chloride (**87**) (140 mg, 0.44 mmol). Phosphoramide (**85**) was obtained as a white solid (62 mg, 35%), m. p. 206-208 °C (from ethyl acetate); $[\alpha]_D^{21}$ = +115.3 (*c* 0.8, chloroform); υ_{max} (nujol)/ cm^{-1} 3239, 2917, 1453, 1180, 1042, 742 and 698; δ_H (270 MHz, $CDCl_3$) 1.53 (3 H, d, J 7, CHC*H*$_3$), 2.13 (3 H, d, J 10.4, NMe), 2.51 (3 H, d, J 9.2, NMe), 2.25 (1 H, br t, J 10.3, NH), 3.91 (2 H, s, C*H*$_2$Ph), 4.27 (1 H, m, C*H*CH$_3$), 6.58 (2 H, d, J 6.8, aryl H), 7.08-7.48 (13 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 26.7 (dq, J_{PC} 8.8), 29.2 (dq, J_{PC} 5.5), 29.6 (dq, J_{PC} 3.3), 51.2 (d), 70.6 (dd, J_{PC} 11), 72.0 (dd, J_{PC} 12.1), 125.6 (d), 126.9 (d), 127.5 (d), 127.8 (d), 128.0 (d), 128.1 (d), 128.2 (d), 128.4 (d), 137.9 (s), 138.1 (d, J_{PC} 6.6), 146.0 (d, J_{PC} 2.2); δ_P (162 MHz, $CDCl_3$) 26.0 (1 P, s); *m/z* (FAB) 406 (M^++1, 100%), 331 (7), 285 (10), 210 (12), 166 (9), 118 (17), 105 (25); (found $[M+H]^+$, 406.2041. $C_{24}H_{29}N_3OP$ requires *m/z*, 406.2048).

Reaction of Phosphoramidic Chlorides with Pyrrolidine.

Preparation of1,3-bis (1-(R)-phenylethyl)-2-pyrrolidyl-1, 3, 2-diazaphospholidine 2-oxide (71).

To a stirred solution of chloride (**68**, R^1= (R)-1-phenylethyl) (200 mg, 0.57 mmol) in DCM (5 cm^3) was added pyrrolidine (0.10 cm^3, 1.14 mmol) dropwise. The resulting mixture was stirred at room temperature for 5 hours. It was then poured into saturated aqueous ammonium chloride solution (2 cm^3) and extracted with DCM (3 x 5 cm^3). The combined organic extracts were dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on silica eluting with 0→10% v/v methanol- DCM to afford triamide (**71**) as a colourless oil (105 mg, 48%) $[\alpha]_D^{20}$= -3.4 (*c* 0.48, chloroform); υ_{max} (film)/ cm^{-1} 3060, 2971, 2856, 1493, 1452, 1392, 1345, 1279, 1214, 1132, 1083, 1037, 1015, 780 and 700; δ_H (270 MHz, $CDCl_3$) 1.54 (3 H, d, J 6.8, CHC*H*$_3$), 1.58 (3 H, d, J 7, CHC*H*$_3$), 1.75 (4 H, m, pyrrolidyl C*H*$_2$), 2.74-3.02 (6 H, m, C*H*$_2$ and pyrrolidyl C*H*$_2$), 3.11-3.25 (2 H, m, C*H*$_2$), 4.31 (2 H, m, C*H*CH$_3$), 7.21-7.41 (10 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) 19.9 (q), 20.2 (q), 26.3 (dt, J_{PC} 9.2), 41.5 (dt, J_{PC} 12.8), 42.6 (dt, J_{PC} 10.9), 46.4 (dt, J_{PC} 5.5), 54.1 (dd, J_{PC} 5.4), 54.4 (dd, J_{PC} 3.7), 126.8 (d), 126.9 (d), 127.0 (d), 128.2 (d), 143.2 (d, J_{PC} 5.5), 143.6 (d, J_{PC} 3.7); δ_P (162 MHz, $CDCl_3$) 20.0 (1 P, s); *m/z* (CI) 384 (M^++1, 100%), 278 (14), 195 (8), 105 (57), 91 (19), 70 (43); (found $[M]^+$, 383.2045. $C_{22}H_{30}N_3OP$ requires *m/z*, 383.2126).

1, 3-dimethyl-4, 5-tetramethylene-2-pyrrolidyl-1, 3, 2-diazaphosphorine 2-oxide (83).

This compound was prepared according to the above procedure using chloride (**74**) (100 mg, 0.45 mmol) and pyrrolidine (0.08 cm^3, 0.9 mmol) in DCM (5 cm^3). Triamide (**83**) was obtained as a white solid (97 mg, 84%), $[\alpha]_D^{22}$= -85 (*c*

0.32 chloroform); υ_{max} (film)/ cm^{-1} 2932, 2830, 1443, 1337, 1302, 1254, 1227, 1208, 1177, 1157, 1065, 961, 889, 851, 806 and 758; δ_H (270 MHz, $CDCl_3$) 1.05-1.23 (4 H, m, CH_2), 1.73-1.78 (6 H, m, CH_2 and pyrrolidyl CH_2), 1.89 (2 H, br t, J 12.7, pyrrolidyl CH_2), 2.39 (3 H, d, J 11.3, NMe), 2.42-2.57 (4 H, m, CH and NMe), 2.63 (1 H, m, CH), 3.03-3.39 (4 H, m, pyrrolidyl CH_2); δ_C (100 MHz, $CDCl_3$) 24.9 (t), 27.0 (dt, J_{PC} 7.4), 28.9 (dt, J_{PC} 9.2), 29.1 (dq, J_{PC} 9.1), 29.4 (q), 47.2 (dt, J_{PC} 3.7), 63.7 (dd, J_{PC} 7.3), 65.4 (dd, J_{PC} 9.1); δ_P (162 MHz, $CDCl_3$) 27.5 (1 P, s); *m/z* (EI) 257 (M^+, 100%), 188 (12), 70 (28); (found $[M+H]^+$, 258.1743. $C_{12}H_{25}N_3OP$ requires *m/z*, 258.1735).

Preparation of Triamide Catalysts by Reaction of α-Methylbenzylamine with *In Situ* Generated Chlorides (80) and (86).

General Procedure:

The following procedure is typical.

Preparation of R, R-4, 5-tetramethylene-2-(N-1-(R)-phenylethyl)-1, 3, 2-diazaphosphorine-2-oxide (78) via in situ trapping of choride (80).

To a stirred solution of R, R-(-)-cyclohexane-1, 2-diamine (200 mg, 1.75 mmol) and triethylamine (4 equivalents, 0.97 cm^3, 7 mmol) in DCM (20 cm^3) at 0 °C was added phosphorous oxychloride (0.16 cm^3, 1.75 mmol) dropwise. The resulting solution was stirred at 0 °C for 2 hours then warmed to room temperature. R-(+)-α methylbenzylamine (0.24 cm^3, 1.93 mmol) was then added and the mixture stirred for 2 hours at room temperature It was then poured into saturated aqueous ammonium chloride solution (10 cm^3) and extracted with DCM (3 x 5 cm^3). The combined organic extracts were washed with saturated aqueous brine (10 cm^3), dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on silica eluting with 0→10% v/v methanol- DCM. This afforded triamide

(**78**) as a white solid which was further purified by recrystallisation from DCM/ hexane (200 mg, 41%), $[\alpha]_D^{18}$= +57.4 (*c* 0.97, chloroform); υ_{max} (nujol)/ cm^{-1} 3227, 1297, 1193, 1176, 1132, 1073, 1036, 967, 870 and 761; δ_H (400 MHz, $CDCl_3$) 1.28-1.09 (4 H, m, C*H*$_2$), 1.36 (3 H, d, J 6.7, CHC*H*$_3$), 1.46 (1 H, m, C*H*$_2$), 1.55-1.67 (2 H, m, C*H*$_2$), 1.82 (1 H, br d, J 7.3, C*H*$_2$), 1.99 (1 H, br d, J 7.9, C*H*), 2.45 (1 H, m, C*H*), 2.69 (1 H, br s, NH), 2.99 (1 H, br t, J 7.3, NH), 3.25 (1 H, br t, J 7.5, NH), 4.25 (1 H, m, C*H*CH$_3$), 7.15-7.31 (5 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 24.0 (dt, J_{PC} 4.4), 25.8 (dq, J_{PC} 8.8), 30.8 (dt, J_{PC} 11), 31.1 (dt, J_{PC} 13.3), 51.3 (d), 59.2 (dd, J_{PC} 6.6), 60.7 (dd, J_{PC} 5.5), 125.4 (d), 126.9 (d), 128.4 (d), 146.3 (d, J_{PC} 2.2); δ_P (162 MHz, $CDCl_3$) 25.6 (1 P, s); *m/z* (CI) 280 (M^++1, 38%), 264 (8), 147 (7), 120 (27), 105 (100), 91 (9), 79 (22); (found $[M+H]^+$, 280.1581. $C_{14}H_{23}N_3OP$ requires *m/z*, 280.1579).

R, R-4, 5-tetramethylene-2-(N-1-(S)-phenylethyl)-1, 3, 2-diazaphosphorine-2-oxide (79) Via In Situ Trapping of Chloride (80).

This compound was prepared according to the above general procedure using S-(-)-α methylbenzylamine. Triamide (**79**) was obtained as colourless needles (from DCM/ hexane) (195 mg, 40%), m. p. 209-210 °C (d) (from DCM/ hexane); (found C, 59.9; H, 8.0; N, 14.9. $C_{14}H_{22}N_3OP$ requires C, 60.22; H, 7.89; N, 15.05%); $[\alpha]_D^{22}$= -67.8 (*c* 0.5, chloroform); υ_{max} (nujol)/ cm^{-1} 3226, 1297, 1192, 1132, 1073, 1036, 966, 870 and 761; δ_H (270 MHz, $CDCl_3$) 1.04-1.21 (4 H, m, C*H*$_2$), 1.35 (3 H, d, J 6.9, CHC*H*$_3$), 1.37-1.73 (4 H, m, C*H*$_2$), 2.29 (1 H, br d, J 7.2, C*H*), 2.37 (1 H, br d, J 7, C*H*), 2.76-2.93 (3 H, br m, NH), 4.31 (1 H, m, C*H*CH$_3$), 7.11-7.22 (5 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) 24.3 (t), 24.4 (t), 25.3 (dq, J_{PC} 7.3), 30.7 (dt, J_{PC} 11), 31.0 (t), 51.3 (d), 60.3 (dd, J_{PC} 7.3), 61.9 (dt, J_{PC} 5.5), 125.9 (d), 126.9 (d), 128.5 (d), 146.2 d, J_{PC} 2.5); δ_P (162 MHz, $CDCl_3$) 26.2 (1 P, s); *m/z* (EI) 279 (M^+, 10%), 264 (55), 159 (21), 120 (100), 96 (10), 77 (16).

S, S-4, 5-diphenyl-2-(N-1-(R)-phenylethyl)-1, 3, 2-diazaphosphorine-2-oxide (84) Via In Situ Ttrapping of Chloride (86).

This compound was prepared according to the above general procedure using S, S-(-)-1, 2-diphenyl-1, 2-ethylenediamine (200 mg, 0.94 mmol), triethylamine (0.52 cm^3, 3.76 mmol), phosphorus oxychloride (0.09 cm^3, 0.94 mmol) and R-(+)-α methylbenzylamine (0.13 cm^3, 1.03 mmol) in DCM (20 cm^3). Triamide (**84**) was obtained as a white solid (227 mg, 64%), m. p. 140-143 °C (from DCM/ hexane); $[\alpha]_D^{20}$= +48.2 (*c* 1.06, chloroform); υ_{max} (nujol)/ cm^{-1} 3171, 1275, 1208, 1184, 1129, 1084, 1040 and 970; δ_H (270 MHz, $CDCl_3$) 1.46 (3 H, d, J 6.8, CHC*H*$_3$), 2.51 (1 H, br d, J 7.7, NH), 2.85 (1 H, br d, J 11.9, NH), 3.31 (1 H, br t, J 9.8, NH), 4.21 (1 H, d, J 8.8, C*H*Ph), 4.35 (1 H, d, J 8.8, C*H*Ph), 4.52 (1 H, m, C*H*CH$_3$), 6.65 (2 H, d, J 7, aryl H), 7.06-7.19 (9 H, m, aryl H), 7.21-7.41 (4 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) 26.0 (dq, J_{PC} 7.4), 51.5 (d), 65.3 (dd, J_{PC} 7.3), 67.3 (dd, J_{PC} 7.4), 125.8 (d), 126.7 (d), 126.9 (d), 127.3 (d), 127.8 (d), 128.1 (d), 128.3 (d), 128.4 (d), 128.6 (d), 139.4 (d, J_{PC} 12.8), 139.6 (d, J_{PC} 7.3), 146.0 (s); δ_P (162 MHz, $CDCl_3$) 22.3 (1 P, s); *m/z* (CI) 378 (M^++1, 100%), 289 (31), 120 (11), 106 (50), 85 (22); (found $[M+H]^+$, 378.1742. $C_{22}H_{25}N_3OP$ requires *m/z*, 378.1735).

Preparation of Triamide Catalysts by N-Alkylation.

Preparation of N-benzyl triamide (77).

To a stirred solution of a 1:1 mixture of R, R-1, 3-dimethyl-4, 5-tetramethylene-2-(N-1-(R)-phenylethyl)-1, 3, 2-diazaphosphorine 2-oxide and the corresponding S, S, R-diastereoisomer (prepared as described above using chloride (**74**) in racemic form) (100 mg, 0.33 mmol) in anhydrous THF (2 cm^3) at 0 °C was added *n*-butyllithium (1.6 M heaxane solution, 0.22 cm^3, 0.36 mmol) dropwise. The resulting pale yellow solution was stirred at 0 °C for 90 minutes. Benzyl

bromide (0.05 cm^3, 0.36 mmol) was then added and the mixture warmed to room temperature and stirred for 24 hours. It was then poured into saturated aqueous ammonium chloride solution (1 cm^3) and extracted with diethyl ether (3 x 2 cm^3). The combined extracts were dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on silica eluting with 0→5% v/v methanol- DCM to afford a 1:1 mixture of diastereomeric triamides (**77**) as a viscous oil (54 mg, 42%) which appeared to decompose rapidly at room temperature, υ_{max} (chloroform film)/ cm^{-1} 2924, 1198, 1119, 1023, 881 and 694; δ_H (270 MHz, $CDCl_3$) 1.17-1.23 (11 H, m, $CHCH_3$ and CH_2), 1.51 (3 H, d, J 7.1, $CHCH_3$), 1.61-1.98 (8 H, m, CH_2), 2.25-2.51 (12 H, m, NMe), 2.61-2.64 (4 H, m, CH), 3.60 (1H, dd, J 15.5 and 10.5, CH_2), 3.90 (1 H, d, J 10.5, CH_2), 3.94 (1 H, d, J 2.7, CH_2), 4.03 (1 H, dd, J 15.5 and 12.4, CH_2), 4.77 (1H, dq, J 12.8 and 6.6, $CHCH_3$), 5.04 (1 H, dq, J 10.5 and 7.1, $CHCH_3$), 7.01-7.36 (20 H, m, aryl H); *m/z* (CI) 398 (M^++1, 100%), 292 (35), 187 (22), 91 (61).

R, R-1, 3-dimethyl-4, 5-tetramethylene-2-(N, N-dimethylamido)-1, 3, 2-diazaphosphorine 2-oxide (82).

This compound was prepared according to the above procedure using R, R-(-)-4, 5-tetramethylene-2-(N, N-dimethylamido)-1, 3, 2-diazaphosphorine-2-oxide (**81**) (100 mg, 0.49 mmol), *n*-butyllithium (1.5 M hexane solution, 0.8 cm^3, 1.23 mmol) and methyl iodide (0.08 cm^3, 1.23 mmol) in anhydrous THF (3 cm^3). Triamide (**82**) was isolated as a viscous oil which solidified on standing (66 mg, 58%), m. p. 55-58 °C; $[\alpha]_D^{19}$= -58.4 (*c* 1.22, chloroform); υ_{max} (nujol)/ cm^{-1} 2932, 1445, 1291, 1252, 1215, 1181, 1119, 1061, 986, 891 and 806; δ_H (270 MHz, $CDCl_3$) 1.05-1.25 (4 H, m, CH_2), 1.71-1.74 (2 H, m, CH_2), 1.84-1.92 (2 H, m, CH_2), 2.33 (3 H, d, J 11.5, NMe), 2.39 (3 H, d, J 10.6, NMe), 2.46-2.55 (1 H, m, CH), 2.57-2.59 (7 H, d overlapping m, J 9.3, $N(Me)_2$ and CH); δ_C (100 MHz, $CDCl_3$) 24.4 (t), 24.5 (t), 28.3 (q), 28.5 (dt, J_{PC} 10.9), 28.8 (dt, J_{PC} 9.1), 29.1 (q),

36.9 (dq, J_{PC} 3.7), 63.3 (dd, J_{PC} 9.1), 65.5 (dd, J_{PC} 9.1); δ_P (162 MHz, $CDCl_3$) 31.0 (1 P, s); *m/z* (EI) 231 (M^+, 90%), 188 (100), 141 (64), 110 (31), 75 (22), 42 (49); (found $[M+H]^+$, 232.1571. $C_{10}H_{23}N_3OP$ requires *m/z*, 232.1579).

Preparation of Triamide Catalysts by Reaction of a Diamine with N, N-Dimethylphosphoramido Dichloridate.

General procedure:

The following procedure is typical.

R, R-(-)-4, 5-tetramethylene-2-(N, N-dimethylamido)-1, 3, 2-diazaphosphorine-2-oxide (81).

To a stirred solution of R, R-(-)-cyclohexane-1, 2-diamine (562 mg, 4.93 mmol) and triethylamine (1.37 cm^3, 9.86 mmol) in DCM (20 cm^3) at 0 °C was added N, N-dimethylphosphoramido dichloridate (0.58 cm^3, 4.93 mmol) dropwise. The resulting mixture was allowed to warm to room temperature and stirred for 3 hours. It was then poured into saturated aqueous ammonium chloride solution (10 cm^3) and extracted with DCM (3 x 5 cm^3). The combined extracts were dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on silica eluting with 0→5% v/v methanol- DCM to afford triamide (**31**) as a white solid which was further purified by recrystallisation from ethyl acetate (400 mg, 40%), m.p. 188-190 °C; (found C, 47.3; H, 9.2; N, 20.6. $C_8H_{18}N_3OP$ requires C, 47.29; H, 8.87; N, 20.69%); $[\alpha]_D^{21}$ = -30 (*c* 1.05, chloroform); υ_{max} (nujol)/ cm^{-1} 3228, 1319, 1309, 1206, 1168, 1118, 1074, 998 and 891; δ_H (270 MHz, $CDCl_3$) 1.32-1.43 (4 H, m, C*H*$_2$), 1.73 (2 H, br m, C*H*$_2$), 1.86 (2 H, br m, C*H*$_2$), 2.4 (1 H, br s, NH), 2.48 (1 H, br s, NH), 2.69 (6 H, d, J 10.3, NMe), 2.91 (1 H, bt t, J 10, C*H*), 3.12 (1 H, br t, J 10.4, C*H*); δ_C (100 MHz, $CDCl_3$) 24.5 (t), 24.6 (t), 31.3 (dt, J_{PC} 11), 31.4 (dt, J 12.8), 37.1 (q), 60.3 (dd, J_{PC} 9.1), 62.1 (dd, J_{PC} 5.5); δ_P (162 MHz, $CDCl_3$)

29.9 (1 P, s); *m/z* (EI) 203 (M^+, 100%), 160 (46), 44 (24).

Preparation of R, R-1, 3-dimethyl-4, 5-tetramethylene-2-(N, N-dimethylamido)-1, 3, 2-diazaphosphorine 2-oxide (82).

This compound was prepared according to the above general procedure using R, R-(-)-N, N'-Dimethylcyclohexane-1, 2-diamine (**73**) (prepared as described above, 500 mg, 3.52 mmol), triethylamine (1.0 cm^3, 7.04 mmol) and N, N-dimethylphosphoramido dichloridate (0.42 cm^3, 3.52 mmol) in DCM (20 cm^3). Triamide (**82**) was isolated as a viscous oil which solidified on standing (308 mg, 38%). The data for this compound is given above.

3-(Dimethylamino)-1, 2, 5, 6, 7, 7a-hexahydro-2-phenylpyrrolo[1, 2-c][1, 2, 3]diazaphosphole-3-oxide (88) and (89).

These compounds were prepared according to the above general procedure using (S)-2-(anilinomethyl)pyrrolidine (200 mg, 1.14 mmol), triethylamine (0.32 cm^3, 2.28 mmol) and N, N-dimethylphosphoramido dichloridate (0.15 cm^3, 1.2 mmol) in DCM (15 cm^3). This afforded a 1.4:1 mixture of diastereomeric triamides (**88**) and (**89**) (266 mg, 88%) which were readily separable by flash chromatography, eluting with ethyl acetate. The absolute configuration at phosphorus was assigned by comparison with literature data.[75a]

3S, 7aS diastereoisomer(88) isolated as white needles (108 mg, 36%), m. p. 99-101 °C (from cyclohexane) (lit.,[75a] 100 °C); R_f 0.42 (ethyl acetate); $[\alpha]_D^{21} = -20.5$ (*c* 1.08, acetone) (lit.,[75a] $[\alpha]_D^{20} = -25.5$ (*c* 1, acetone)); δ_H (270 MHz, $CDCl_3$) 1.67-2.04 (4 H, m, CH_2), 2.63 (6 H, d, J 10.4, NMe), 2.85-2.99 (1 H, m, CH_2), 3.35-3.41 (1 H, m, CH_2), 3.62-3.84 (3 H, m, 7a-*CH* and CH_2), 6.93 (1 H, t, J 7.3, aryl H), 7.03-7.07 (2 H, m, aryl H), 7.24-7.29 (2 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 26.0

(dt, J_{PC} 2.2), 32.1 (t), 36.2 (dq, J_{PC} 4.4), 45.2 (dt, J_{PC} 2.2), 49.0 (dt, J_{PC} 16.5), 57.9 (dd, J_{PC} 7.7), 115.7 (dd, J_{PC} 5.5), 120.6 (d), 128.9 (d), 142.0 (d, J_{PC} 5.5); *m/z* (EI) 265 (M^+, 100%), 221 (13), 160 (50), 117 (53), 105 (44), 70 (95), 43 (28).

3R, 7aS diastereoisomer (89) isolated as white needles (158 mg, 52%), m. p. 146-149 °C (from cyclohexane/ ethyl acetate) (lit.,[75a] 150 °C); R_f 0.15 (ethyl acetate); $[\alpha]_D^{21}$ = +85.3 (*c* 0.98, acetone) (lit.,[75a] $[\alpha]_D^{20}$ = +86 (*c* 1, acetone)); δ_H (270 MHz, $CDCl_3$) 1.61-1.68 (1 H, m, C*H*$_2$), 1.96-2.18 (3 H, m, C*H*$_2$), 2.62 (6 H, d, J 10.1, NMe), 3.11-3.32 (3 H, m, C*H*$_2$), 3.67-3.77 (1 H, m, C*H*$_2$), 4.01-4.08 (1 H, m, 7a-C*H*), 6.92 (1 H, t, J 7.3, aryl H), 7.04-7.21 (2 H, m, aryl H), 7.24-7.28 (2 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 27.3 (dt, J_{PC} 5.5), 31.6 (dt, J_{PC} 4.4), 36.7 (q), 43.5 (dt, J_{PC} 4.3), 52.3 (dt, J_{PC} 12.1), 56.4 (dd, J_{PC} 8.7), 114.8 (dd, J_{PC} 4.4), 120.8 (d), 129.0 (d), 142.6 (d, J_{PC} 6.6); *m/z* (EI) 265 (M^+, 100%), 221 (14), 160 (48), 149 (20), 117 (55), 70 (100), 43 (68).

Preparation of 2-chloro-1, 3-dimethyl-1, 3, 2-diazaphospholane.

This compound was prepared by a literature procedure.[69,70] To a stirred solution of N, N'-dimethylethylenediamine (5.0 g, 56.8 mmol) and triethylamine (15.8 cm^3, 113.6 mmol) in anhydrous diethyl ether (100 cm^3) at -78 °C was added phosphorus trichloride (5.0 cm^3, 56.8 mmol) dropwise over 10 minutes. The mixture was warmed to room temperature and stirred for 2 hours. The amine hydrochloride precipitate was filtered off and the solids washed with anhydrous diethyl ether (3 x 30 cm^3). The combined washings were then concentrated *in vacuo* to afford the chloride as a pale yellow oil which was purified by distillation under reduced pressure (6.95 g, 80%), b. p. 78-82 °C (0.5 mmHg) (lit.,[69] 70 °C, 0.2 mmHg); δ_H (270 MHz, $CDCl_3$) 2.72 (6 H, d, J 14.6, NMe), 3.31 (4 H, m, C*H*$_2$).

Attempted Preparation of Triaminophosphines by Reaction of 2-chloro-1, 3-dimethyl-1, 3, 2-diazaphospholane with Hindered Secondary Amines (Scheme 30).

The following sequence was attempted using both 2, 2, 6, 6-tetramethylpiperidine and diisopropylamine and is based on a literature procedure.[69]

To a stirred solution of 2-chloro-1, 3-dimethyl-1, 3, 2-diazaphospholane (6.0 g, 39.2 mmol) in diethyl ether (100 cm^3) at -78 ^oC was added the amine (2 equivalents, 78.4 mmol) dropwise over 10 minutes. The resulting mixture was warmed slowly to room temperature and stirred for 2 hours. The amine hydrochloride precipitate was filtered off and the solids washed with diethyl ether (3 x 30 cm^3). The combined washings were then concentrated *in vacuo*. The residue was a dark brown oil. NMR analysis of the crude product indicated mainly decomposition products with none of the reqiured triaminophosphine being present.

Section 4.6 Improved Ketone Binding.

4.6.1 Amino Alcohol Derived Phosphinamides.

General Procedure:

The following procedure is typical.

Preparation of N-diphenylphosphinyl protected norephedrine (93).

To a stirred solution of 1R, 2S-(-)-norephedrine (1.62 g, 10.7 mmol) and triethylamine (2.23 cm^3, 16.05 mmol) in DCM (20 cm^3) at 0 °C was added diphenylphosphinic chloride (2.04 cm^3, 10.7 mmol) dropwise over 5 minutes. The mixture was stirred at 0 °C for 1 hour then warmed to room temperature and stirred for a further 6 hours. It was then poured into saturated aqueous ammonium chloride solution (10 cm^3) and extracted with DCM (3 x 10 cm^3). The combined extracts were washed with saturated aqueous brine (10 cm^3), dried (magnesium sulfate) and concentrated *in vacuo*. The residue was recrystallised from DCM/ hexane to afford phosphinamide (**93**) as white needles (3.42 g, 91%), m. p. 138-140 °C; (found C, 71.5; H, 6.3; N, 3.9. $C_{21}H_{22}NO_2P$ requires C, 71.79; H, 6.27; N, 3.99%); $[\alpha]_D^{25}$= -58.3 (*c* 1.07, chloroform); υ_{max} (nujol)/ cm^{-1} 3200, 1167, 9714, 751, 724 and 697; δ_H (270 MHz, $CDCl_3$) 1.01 (3 H, d, J 6.8, CHC*H*3), 3.11-3.16 (1 H, m, NH), 3.37-3.39 (1 H, m, C*H*CH3), 4.75 (1 H, br s, C*H*Ph), 5.87 (1 H, br s, OH), 7.12-7.46 (11 H, m, aryl H), 7.71-7.88 (4 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) 17.7 (dq, J_{PC} 7.3), 53.8 (d), 76.7 (dd, J_{PC} 5.5), 126.7, 126.9, 127.8, 128.4, 128.5, 128.6, 131.5, 131.6, 131.9, 132.4, 132.5, 141.1 (s); δ_P (162 MHz, $CDCl_3$) 25.2 (1 P, s); *m/z* (CI) 352 (M^++1, 100%), 334 (29), 245 (37), 201 (20), 134 (22), 107 (10); (found $[M+H]^+$, 352.1473. $C_{21}H_{23}NO_2P$ requires *m/z*, 352.1466).

N-diphenylphosphinyl protected ephedrine (94).

This compound was prepared according to the above general procedure using 1R, 2S-ephedrine (1.77 g, 10.7 mmol). Chromatography on silica, eluting with 0→5% v/v methanol- DCM afforded phosphinamide (**94**) as a white solid (1.17 g, 30%), m. p. 190-191 °C (from ethyl acetate); (found C, 72.1; H, 6.6; N, 3.8. $C_{22}H_{24}NO_2P$ requires C, 72.33; H, 6.58; N, 3.84%); $[\alpha]_D^{20}$= -2.7 (*c* 0.74, chloroform); υ_{max} (nujol)/ cm^{-1} 3300, 2850, 1601,1502, 1438,,1121, 995, 753, 727 and 696; δ_H (270 MHz, $CDCl_3$) 1.31 (3 H, d, J 7, $CHCH_3$), 2.43 (3 H, d, J 10.8, NMe), 3.67 (1 H, m, $CHCH_3$), 4.71 (1 H, br s, OH), 4.84-4.86 (1 H, m, CHPh), 7.39-7.67 (15 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) 13.6 (q), 31.0 (q), 58.0 (d), 76.7 (dd, J_{PC} 18.3), 126.5, 127.2, 128.0, 128.4, 128.5, 128.6, 130.7 (s), 131.1 (s), 131.8, 132.1, 132.2, 132.3, 132.35, 132.4, 142.6 (s); δ_P (162 MHz, $CDCl_3$) 34.3 (1 P, s); *m/z* (CI) 366 (M^++1, 100%), 348 (61), 258 (82), 203 (67), 148 (38), 107 (67).

N-diphenylphosphinyl protected valinol(92).

This compound was prepared according to the above general procedure using S-valinol (1.0 g, 9.71 mmol), triethylamine (2.03 cm^3, 14.57 mmol) and diphenylphosphinic chloride (1.85 cm^3, 9.71 mmol) in DCM (25 cm^3). Chromatography on silica, eluting with 0→10% v/v methanol- DCM afforded phosphinamide (**92**) as a white solid (2.21 g, 75%), m. p. 135-137 °C (from diethyl ether); (found C, 67.2; H, 7.3; N, 4.3. $C_{17}H_{22}NO_2P$ requires C, 67.31; H, 7.31; N, 4.62%); $[\alpha]_D^{21}$= -40.5 (*c 1*, methanol); υ_{max} (nujol)/ cm^{-1} 3260, 1380, 1172, 725 and 691; δ_H (400 MHz, $CDCl_3$) 0.94 (3 H, d, J 6.7, $(CH_3)_2CH$), 0.96 (3 H, d, J 7, $(CH_3)_2CH$), 1.81 (1 H, sep, J 6.7, $(CH_3)_2CH$), 2.81-2.84 (1H, m, CH), 3.02 (1 H, br dd, J 11.3 and 3.4, NH), 3.52 (1 H, dd, J 11.9 and 8, CH_2), 3.69 (1 H, br d, J 11, CH_2), 5.16 (1 H, br s, OH), 7.27-7.52 (6 H, m, aryl H), 7.77-7.96 (4 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) 18.5 (q), 19.8 (q), 31.2 (dd, J_{PC} 10.9), 60.8 (d), 66.1 (t),

128.3, 128.5, 128.6, 128.7, 129.9 (s), 131.2 (s), 131.7, 131.8, 131.9, 132.2, 132.8, 132.9; δ_P (162 MHz, $CDCl_3$) 26.3 (1 P, s); *m/z* (CI) 304 (M^++1, 100%), 286 (5), 272 (16), 201 (11) 85 (9).

N-diphenylphosphinyl protected prolinol(95).

This compound was prepared according to the above general procedure using S-prolinol (0.42 cm^3, 4.16 mmol), triethylamine (0.87 cm^3, 6.24 mmol) and diphenylphosphinic chloride (0.81 cm^3, 4.16 mmol) in DCM (20 cm^3). Chromatography on silica, eluting with 0→10% v/v methanol- DCM afforded phosphinamide (**95**) as a viscous oil which solidified on standing (1.01 g, 81%), m. p. 98-99 °C (from DCM/ hexane);(found C, 67.5; H, 6.7; N, 4.6. $C_{17}H_{20}NO_2P$ requires C, 67.77; H, 6.64; N, 4.65%); $[\alpha]_D^{18}$= +48.2 (*c* 1.06, chloroform); υ_{max} (nujol)/ cm^{-1} 3325, 1723, 1592, 1521, 1439, 1212, 1123, 774 and 669; δ_H (270 MHz, $CDCl_3$) 1.60-2.05 (4 H, m, CH_2), 2.99-3.07 (2 H, m, CH_2), 3.34-3.46 (2 H, m, CH_2), 3.63-3.65 (1 H, m, CH), 4.92 (1 H, br m, OH), 7.2-7.84 (10 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) 25.1 (dt, J_{PC} 12.8), 29.3 (dt, J_{PC} 7.3), 48.3 (dt, J_{PC} 3.7), 61.3 (d), 65.2 (t), 128.3, 128.4, 128.5, 128.6, 131.35, 131.4, 131.6, 131.8, 131.9, 132.2, 132.25, 132.3; δ_P (162 MHz, $CDCl_3$) 27.5 (1 P, s); *m/z* (FAB) 302 (M^++1, 63%), 270 (15), 201 (34), 167 (15), 149 (100), 113 (19); (found $[M+H]^+$, 302.1316. $C_{17}H_{21}NO_2P$ requires *m/z*, 302.1310).

N-diphenylphosphinyl protected 2-amino-1-phenylethanol (147).

This compound was prepared according to the above general method using 2-amino-1-phenylethanol (1.0 g, 7.3 mmol), triethylamine (1.52 cm^3, 10.95 mmol) and diphenylphosphinic chloride (1.39 cm^3, 7.3 mmol) in DCM (20 cm^3). Phosphinamide (**147**) was obtained as a white solid (2.18 g, 89%), m. p. 159-161 °C (from DCM/ hexane); (found C, 70.7; H, 6.0; N, 4.1. $C_{20}H_{20}NO_2P$ requires C

71.21; H, 5.98; N, 4.15%); υ_{max} (nujol)/ cm^{-1} 3266, 3168, 1169, 1119, 1068, 921, 871, 725 and 694; δ_H (270 MHz, $CDCl_3$) 3.09-3.81 (2 H, m, C*H*$_2$), 3.82 (1 H, br d, J 6.8, NH), 4.88 (1 H, dd, J 7.5 and 3, C*H*Ph), 7.22-7.46 (12 H, m, aryl and OH), 7.75-7.83 (4 H, m, aryl H); δ_C (100 MHz, DMSO-d^6) 55.0 (t), 73.2 (dd, J_{PC} 7.3), 126.2, 127.1, 128.0, 128.5, 128.6, 131.6, 131.65, 131.8, 131.85, 131.9, 132.6 (d, J_{PC} 20), 134.0 (d, J_{PC} 20), 143.4 (s); δ_P (162 MHz, $CDCl_3$) 23.4 (1 P, s); *m/z* (CI) 338 (M^++1, 22%), 320 (22), 231 (93), 202 (100), 155 (21), 107 (25), 77 (49).

Preparation of t-BDPS-protected phosphinamide (96).

To a stirred solution of alcohol (**95**) (200 mg, 0.66 mmol) and imidazole (68 mg, 1 mmol) in DMF (1.5 cm^3) was added *t*-butyldiphenylsilyl chloride (0.16 cm^3, 0.62 mmol). The pale yellow solution was stirred at room temperature for 18 hours. It was then poured into saturated aqueous ammonium chloride solution (1 cm^3) and extracted with ethyl acetate (3 x 2 cm^3). The combined extracts were washed with water (2 x 2 cm^3) then dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on silica eluting with 0→70% v/v ethyl acetate- petrol to afford silyl protected phosphinamide (**96**) as a colourless oil which solidified on standing (260 mg, 78%), m. p. 101-102 °C (from diethyl ether); $[\alpha]_D^{17}$= -5.8 (*c* 1.04, chloroform); υ_{max} (nujol)/ cm^{-1} 2964, 1520, 1472, 1438, 1112, 754, 714 and 671; δ_H (400 MHz, $CDCl_3$) 0.72 (9 H, s, CMe_3), 1.58 (2 H, m, C*H*$_2$), 1.71-1.85 (2 H, m, C*H*$_2$), 2.78-2.91 (1 H, m, C*H*$_2$), 2.92-3.01 (1 H, m, C*H*$_2$), 3.07 (1 H, dd, J 6.6 and 5, C*H*$_2$), 3.15 (1 H, dd, J 6.5 and 3, C*H*$_2$) 3.51 (1 H, m, C*H*), 7.01-7.24 (14 H, m, aryl H), 7.33 (2 H, dd, J 7.9 and 1.5, aryl H), 7.41-7.51 (2 H, m, aryl H), 7.56-7.62 (2 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 19.1 (s), 25.2 (dt, J_{PC} 5.5), 26.7 (q), 29.0 (dt, J_{PC} 4.4), 47.8 (t), 59.1 (d), 65.7 (dt, J_{PC} 4.4), 127.5, 128.0, 128.3, 128.45, 128.5, 129.5, 131.4, 131.5, 132.0, 132.1, 132.3, 132.4, 133.3 (s), 133.4 (s), 133.5 (s), 135.3, 135.5; δ_P (162 MHz, $CDCl_3$) 27.0 (1 P, s); *m/z* (FAB) 540 (M^++1, 50%), 482 (31), 462 (100), 270 (42), 201 (95), 135 (30); (found $[M+H]^+$, 540.2496.

$C_{33}H_{39}NO_2SiP$ requires *m/z*, 540.2488).

Reduction Procedure Using Amino Alcohol Derived Phosphinamides.

The general procedure described in Section 4.1 was employed for examination of these catalyst systems. The precomplexation studies were carried out using the norephedrine derived phosphinamide (**93**) as described below.

To a stirred solution of phosphinamide (**93**) (2 mol%, 0.05 mmol, 17.6 mg) in THF (2.5 cm^3) was added BMS (10 M dimethyl sulfide complex, 5.5 µl, 0.055 mmol) dropwise. Vigorous effervescence was observed. The mixture was stirred at room temperature for 8 hours. Acetophenone (0.3 cm^3, 2.57 mmol) was then added, followed by BMS (10 M, dimethyl sulfide complex, 0.15 cm^3, 1.54 mmol). The solution was then stirred at room temperature for 2.5 hours. The reaction mixture was then worked up and the alcohol isolated and purified as described in Section 4.1. 1-Phenylethanol was obtained as a colourless oil (235 mg, 75%), $[\alpha]_D^{21} = -4.7$ (*c* 1, methanol), 11% e.e. (S).[40]; δ_H (270 MHz, $CDCl_3$) 1.47 (3 H, d, J 6, $CHCH_3$), 2.15 (1 H, br s, OH), 4.85 (1 H, q, J 6.4, $CHCH_3$), 7.22-7.37 (5H, m, aryl H).

4.6.2 Chiral Diols/ Phosphinamide Donors.

***In Situ* Generation of Boronate Esters.**

General Procedure:

The following procedure is typical.

Generation of Boronate (98, R=Me).

To a stirred solution of R, R-(-)-butanediol (**97**, R=Me) (0.02 cm^3, 0.22 mmol) in THF (0.25 cm^3) was added BMS (10 M dimethyl sulfide complex, 0.024 cm^3, 0.24 mmol) dropwise. Vigorous effervescence was observed. The mixture was then stirred at room temperature for 20 minutes. This solution was used immediately as described below.

Boronate (98, R=Ph).

This was generated according to the above procedure using R, R-(+)-dihydrobenzoin (**97**, R=Ph) (48 mg, 0.22 mmol). The solution was used immediately as described below.

Boronate (104).

This was generated according to the above procedure using L-(+)-diethyltartrate (46 mg, 0.22 mmol). The solution was used immediately as described below.

Boronate (105).

This was generated according to the above procedure using S, S-(-)-tetramethyl-D-tartaramide (45 mg, 0.22 mmol). The solution was used immediately as described below.

Boronate (102).

This was prepared according to the above procedure using R, R-(-)-butanediol (0.02 cm^3, 0.22 mmol) and monochloroborane (dimethyl sulfide

complex, 0.026 cm^3, 0.26 mmol) in THF (0.25 cm^3). The solution was used immediately as described below.

*Diamine/ Borane Complex (**106**).*

This was prepared according to the above procedure using S, S-(-)-N, N'-dimethyl-1, 2-diphenylethylene-1, 2-diamine (prepared as described in Section 4.5) (50 mg, 0.22 mmol). The solution was used immediately as described below.

*Preparation of Boronate (**103**).*

This preparation was based on a literature procedure.[83,116] To a stirred solution of R, R-(+)-hydrobenzoin (**97**, R=Ph) (40 mg, 0.19 mmol) in pentane (1.5 cm^3) was added butylboronic acid (18 mg, 0.19 mmol). The solution was stirred at room temperature for 5 minutes. Solid sodium sulfate was then added (ca. 0.5 g) and the mixture filtered. The filtrate was concentrated *in vacuo* to give boronate (**103**) as a colourless oil which solidified on standing (51 mg, 95%), δ_H (270 MHz, $CDCl_3$) 0.95 (3 H, t, J 7.1, C*H*$_3$), 1.36-1.61 (6 H, m, C*H*$_2$), 5.15 (2 H, s, C*H*Ph), 7.26-7.42 (10 H, m, aryl H). The crude product was used immediately without further purification.

Reduction Catalysed by Boronate Complexes in Combination with Phosphinamide (29).

The following is a typical procedure. Reaction times, yields and selectivities obtained with the above boronate complexes are described in the text (Section 2.6.2).

To a solution of boronate ester (**98**, R=Me), prepared as described above (0.22 mmol in THF), was added phosphinamide (**29**) (70 mg, 0.22 mmol)

portionwise under a rapid stream of nitrogen. Acetophenone (0.26 cm^3, 2.2 mmol) was then added followed by BMS (10 M dimethyl sulfide complex, 0.13 cm^3, 1.32 mmol) dropwise. The resulting solution was stirred at room temperature for 90 minutes. The reaction mixture was then worked up and the alcohol isolated and purified as described in Section 4.1. 1-Phenylethanol was obtained as a colourless oil (239 mg, 89%), $[\alpha]_D^{22}$= -20.2 (*c* 1, methanol), 47% e.e. (S).[40]; δ_H (270 MHz, $CDCl_3$) 1.47 (3 H, d, J 6, $CHCH_3$), 2.15 (1 H, br s, OH), 4.85 (1 H, q, J 6.4, $CHCH_3$), 7.22-7.37 (5H, m, aryl H).

Reduction Catalysed by Boronates (98, R=Ph) and (98, R=Me).

The following is a typical procedure. Reaction times, yields and selectivities are described in the text (Section 2.6.2).

To a solution of boronate ester (**98**, R=Ph), prepared as described above (0.22 mmol in THF), was added acetophenone (0.026 cm^3, 0.22 mmol) followed by BMS (10 M, dimethyl sulfide complex, 0.013 cm^3, 0.13 mmol) dropwise. The resulting solution was stirred at room temperature for 3 hours. The reaction mixture was then worked up and the alcohol isolated and purified as described in Section 4.1. 1-Phenylethanol was obtained as a colourless oil (24 mg, 90%), $[\alpha]_D^{20}$= -18.1 (*c* 1, methanol); δ_H (270 MHz, $CDCl_3$) 1.47 (3 H, d, J 6, $CHCH_3$), 2.15 (1 H, br s, OH), 4.85 (1 H, q, J 6.4, $CHCH_3$), 7.22-7.37 (5H, m, aryl H).

*Preparation of N-benzyldiphenylphosphinamide (**101**).*

To a stirred solution of benzylamine (0.46 cm^3, 4.2 mmol) and triethylamine (1.17 cm^3, 8.4 mmol) in DCM (20 cm^3) at 0°C was added diphenylphosphinic chloride (0.81 cm^3, 4.2 mmol) dropwise. The resulting mixture was warmed to room temperature and stirred overnight. It was then poured into an equal volume of saturated aqueous ammonium chloride solution and extracted with DCM (3 x 10

cm^3). The combined extracts were then dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on silica eluting with 0→10% v/v methanol-DCM to afford phosphinamide (**101**) as a white solid (1.18 g, 91%), m. p. 102-104 °C (from DCM/ petrol); (found C, 74.1; H, 5.9; N, 4.6. $C_{19}H_{18}NOP$ requires C, 74.27; H, 5.86; N, 4.56%); υ_{max} (nujol)/ cm^{-1} 3200, 1589, 1178, 1125, 1063, 1026, 997, 909, 859, 726 and 699; δ_H (270 MHz, $CDCl_3$) 3.31 (1 H, br d, J 5.6, NH), 4.11 (2 H, t, J 7.5, CH_2), 7.24-7.52 (11 H, m, aryl H), 7.89-7.97 (4 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) 44.3 (t), 127.0, 128.1, 128.2, 128.3, 131.5, 131.8, 131.9, 132,7 (s), 139.5 (d, J_{PC} 7.3); δ_P (162 MHZ, $CDCl_3$) 23.6 (1 P, s); *m/z* (CI) 308 (M^++1, 92%), 233 (38), 203 (63), 148 (45), 106 (100), 91 (77), 77 (35).

4.6.3 Phosphinamide/ Diol as a Single Molecular Entity.

4.6.3.1 Preparation of Phosphinamide Diols by Asymmetric Dihydroxylation.

Preparation of Alkenes.

General Procedure:

The following procedure is typical.

Preparation of Phosphinamide alkene (109).

To a stirred solution of phosphinamide (**29**) (1.0 g, 3.11 mmol) in anhydrous THF (45 cm^3) at 0 °C was added *n*-butyllithium (2.38 M hexane solution, 1.57 cm^3, 3.73 mmol) dropwise over 5 minutes. The resulting pale yellow solution was warmed to room temperature and stirred for 1 hour. Allyl bromide (0.29 cm^3, 3.42 mmol) was added and the mixture stirred for 18 hours. It was then poured into saturated aqueous ammonium chloride solution (20 cm^3) and extracted with DCM (3 x 10 cm^3). The combined extracts were then dried (magnesium sulfate) and

concentrated *in vacuo*. The residue was purified on silica eluting with 0→50% v/v ethyl acetate- petrol to afford alkene (**109**) as a white solid (882 mg, 79%), m. p. 88-90 °C (from DCM/ hexane); (found C, 76.2; H, 6.75; N, 3.9. $C_{23}H_{24}NOP$ requires C, 76.45; H, 6.65; N, 3.88%); $[\alpha]_D^{18}$= +41.0 (*c* 1.53, chloroform); υ_{max} (nujol)/ cm^{-1} 1590, 1120, 1027, 916, 732 and 698; δ_H (270 MHz, $CDCl_3$) 1.62 (3 H, d, J 7.1, CHC*H*$_3$), 3.26-3.41 (1 H, m, C*H*$_2$), 3.49-3.53 (1 H, m, C*H*$_2$), 4.59 (1 H, dd, J 17.2 and 2.7, alkene C*H*), 4.73-4.77 (2 H, m, alkene C*H*), 5.61 (1 H, m, C*H*CH$_3$), 7.22-7.47 (11 H, m, aryl H), 7.88-7.97 (4 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 19.4 (dq, J_{PC} 3.3), 46.4 (dt, J_{PC} 3.3), 54.4 (dd, J_{PC} 4.4), 115.8 (t), 121.1, 128.1, 128.2, 128.4, 131.6, 132.4, 132.45, 132.6, 133.2 (s), 133.3 (s), 137.6, 137.7, 141.2 (d, J_{PC} 4.4); δ_P (162 MHz, $CDCl_3$) 31.3 (1 P, s); *m/z* (CI) 362 (M^++1, 100%), 346 (16), 320 (88), 256 (40), 201 (66), 160 (25), 105 (33), 77 (22).

Phosphinamide Alkene (111).

This compound was prepared according to the above general procedure using phosphinamide (**29**) (275 mg, 0.86 mmol), *n*-butyllithium (2.38 M, 0.43 cm^3, 1.03 mmol) and cinnamyl bromide (0.14 cm^3, 0.94 mmol) in anhydrous THF (15 cm^3). Alkene (**111**) was isolated as a white solid (326 mg, 87%), m. p. 98-100 °C (from DCM/ hexane); (found C, 79.3; H, 6.5; N, 3.2. $C_{29}H_{28}NOP$ requires C, 79.63; H, 6.41; N, 3.20%); $[\alpha]_D^{18}$= +6.3 (*c* 0.51, chloroform); υ_{max} (nujol)/ cm^{-1} 1588, 1206, 1137, 1117, 1101, 1067, 969, 898, 727 and 699; δ_H (270 MHz, $CDCl_3$) 1.64 (3 H, d, J 7, CHC*H*$_3$), 3.52 (1 H, ddd, J 16.3, 11 and 6.6, C*H*$_2$), 3.69 (1 H, ddd, J 16, 10.8 and 5, C*H*$_2$), 4.79 (1 H, dq, J 10 and 7.5, C*H*CH$_3$), 5.73-5.83 (2 H, m, alkene C*H*), 7.08-7.51 (16 H, m, aryl H), 7.91-8.01 (4 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 19.3 (q), 45.9 (dt, J_{PC} 4.3), 54.2 (dd, J_{PC} 4.4), 126.2, 127.25, 127.3, 128.3, 128.4, 128.5, 128.6, 128.9, 131.0, 131.7, 131.75, 132.5, 132.7, 133.5 (s), 136.8 (s), 141.4 (d, J_{PC} 4.3); δ_P (162 MHz, $CDCl_3$) 31.3 (1 P, s); *m/z* (EI) 437 (M^+, 42%), 422 (31), 332 (100), 201 (79), 117 (32), 77 (31).

Phosphinamide Alkene (112).

This compound was prepared according to the above general procedure using phosphinamide (**29**) (300 mg, 0.93 mmol), *n*-butyllithium (2.38 M hexane solution, 0.47 cm^3, 1.12 mmol) and prenyl bromide (0.12 cm^3, 1.03 mmol) in anhydrous THF (15 cm^3). Alkene (**112**) was obtained as a white solid (268 mg, 74%), m. p. 50-52 °C (from DCM/ hexane); (found C, 76.9; H, 7.2; N, 3.6. $C_{25}H_{28}NOP$ requires C, 77.12; H, 7.20; N, 3.60%); $[\alpha]_D^{18}$= +24.1 (*c* 1.05, chloroform); υ_{max} (nujol)/ cm^{-1} 1312, 1170, 1119, 1071, 996, 973, 895, 751, 725 and 698; δ_H (270 MHz, $CDCl_3$) 1.04 (3 H, s, C*H*$_3$), 1.47 (3 H, s, C*H*$_3$), 1.62 (3 H, d, J 7.2, CHC*H*$_3$), 3.31-3.53 (2 H, m, C*H*$_2$), 4.71 (1 H, dq, J 10.2 and 7.2, C*H*CH_3), 4.97 (1 H, br m, alkene C*H*), 7.21-7.54 (11 H, m, aryl H), 7.93-8.0 (4 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 17.1 (q), 19.2 (dq, J_{PC} 3.25), 25.5 (q), 41.4 (dt, J_{PC} 3.3), 54.2 (dd, J_{PC} 3.3), 60.3 (s), 124.0, 124.1, 126.95, 128.05, 128.1, 128.2, 128.3, 131.4, 132.4, 132.5, 132.6, 132.65, 133.5 (s), 133.6 (s), 141.5 (d, J_{PC} 4.4); δ_P (162 MHz, $CDCl_3$) 31.1 (1 P, s); *m/z* (EI) 389 (M^+, 37%), 320 (10), 284 (45), 201 (50), 151 (32), 133 (42), 42 (100).

Oxidation of Alkenes.

General Procedure:

The following procedure is typical.

Preparation of Diastereomerically Enriched Phosphinamide Diol ent. (127).

To a rapidly stirred solution of AD-mix-β[88,89] (388 mg), potassium osmate(VI) dihydrate (ca. 2 mg) and methanesulfonamide (26 mg, 0.28 mmol) in 1:1 *t*-butanol/ water (1.4 cm^3 of each) at 0 °C was added alkene (**109**) (100 mg,

0.28 mmol). The mixture was stirred for 5 hours at 0 °C, by which time all of the alkene had been consumed (by TLC). Sodium metabisulfite (450 mg) was then added with vigorous stirring and the mixture warmed slowly to room temperature. The mixture was then diluted with ethyl acetate (5 cm^3) and the aqueous phase extracted with ethyl acetate (4 x 2 cm^3). The combined extracts were washed with 1 M aqueous sodium hydroxide solution (5 cm^3), dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on silica eluting with 0→10% v/v methanol- DCM to afford the phosphinamide diol as a white foam (99 mg, 91%). This consisted of an inseparable 1.7:1 mixture of R, R- and R, S-diastereoisomers (as assessed by ^1H and ^{31}P NMR) with the R, R-diastereoisomer being in excess. The diol configuration was assigned by comparison of NMR data with a pure sample of the corresponding R, S-diastereoisomer prepared by a different route (see below).

R, R-diastereoisomer: δ_H (270 MHz, $CDCl_3$) 1.65 (3 H, d, J 7, $CHCH_3$), 2.81 (1 H, br s, OH), 2.82-3.17 (3 H, m, CH_2), 3.19-3.31 (2 H, m, CH_2 and CHOH), 4.56-4.62 (1 H, m, $CHCH_3$), 5.47 (1 H, br s, OH), 7.01-7.64 (11 H, m, aryl H), 7.92-8.02 (4 H, m, aryl H); δ_P (162 MHz, $CDCl_3$) 34.6 (1 P, s); R, S-diastereoisomer: δ_H (270 MHz, $CDCl_3$) 1.57 (3 H, d, J 7, $CHCH_3$), 2.64 (1 H, br m, OH), 2.98-3.09 (2 H, m, CH_2), 3.25-3.42 (2 H, m, CH_2), 3.63-3.71 (1 H, m, CHOH), 4.45 (1 H, m, $CHCH_3$), 5.41 (1 H, br m, OH), 7.25-7.55 (11 H, m, aryl H), 7.78-7.91 (4 H, m, aryl H); δ_P (162 MHz, $CDCl_3$) 35.7 (1 P, s).

Full data for pure samples of the R, S-diastereoisomer (**107**) and the enantiomer of the R, R-diastereoisomer (i.e. S, S-phosphinamide diol (**127**)) prepared by a different route is given below.

Oxidation of alkene (109) with AD-mix-α.

Repeating the above reaction using AD-mix-α[88,89] (308 mg), potassium osmate(VI) dihydrate (ca. 2 mg), methanesulfonamide (21 mg, 0.22 mmol) and

alkene (**109**) (80 mg, 0.22 mmol) in 1:1 *t*-butanol/ water (1 cm^3 of each) gave a mixture of phosphinamide diols (62 mg, 72%) in an identical ratio to that obtained with AD-mix-β (1.7:1), with the R, R-diastereoisomer again being in excess

Oxidation of alkene (109) without phthalazine ligand.

Repeating the above reaction using potassium ferricyanide (980 mg, 2.98 mmol), potassium carbonate (411 mg, 2.98 mmol), potassium osmate(VI) dihydrate (ca. 4 mg), methanesulfonamide (95 mg, 1 mmol) and alkene (**109**) (360 mg, 1 mmol) in 1:1 *t*-butanol/ water (5 cm^3 of each) gave a mixture of phosphinamide diols (292 mg, 74%) in an identical ratio to that obtained with AD-mix- α or β (1.7:1), with the R, R-diastereoisomer again being in excess.

Preparation of α-Hydroxy Ketones (113).

Oxidation of alkene (**111**) (300 mg, 0.69 mmol) according to the above general method using AD-mix-β[88,89] (420 mg), potassium osmate(VI) dihydrate (ca. 2 mg) and methanesulfonamide (29 mg, 0.69 mmol) in 1:1 *t*-butanol/ water (1.5 cm^3 of each) gave an inseparable 1.3:1 mixture of diastereomeric α-hydroxy ketones (**113**) as a white foam (246 mg, 76%), υ_{max} (chloroform film)/ cm^{-1} 3319, 3060, 2932, 1494, 1439, 1173, 1121, 909, 728 and 699; δ_H ($CDCl_3$) major diastereoisomer: 1.39 (3 H, d, J 7, $CHCH_3$), 2.96-3.11 (2 H, m, CH_2), 4.05-4.09 (1 H, m, CHOH), 4.38 (1 H, dq, J 10.4 and 7.1, $CHCH_3$), 5.81 (1 H, br d, J 2.4, OH), 7.23-7.56 (15 H, m, aryl H), 7.84-7.93 (5 H, m, aryl H); minor diastereoisomer: 1.63 (3 H, d, J 7, $CHCH_3$), 2.98-3.14 (1 H, m, CH_2), 3.52 (1 H, ddd, J 15, 13.5 and 3, CH_2), 4.30 (1 H, br d, J 10, CHOH), 4.59 (1 H, dq, J 10.2 and 7, $CHCH_3$), 5.56 (1 H, br d, J 2.4, OH), 7.22-7.54 (15 H, m, aryl H), 7.88-8.04 (5 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) major diastereoisomer: 17.6 (q), 47.0 (t), 54.8 (dd, J_{PC} 5.5), 75.2 (d), 126.2-141.3 (aryl C) (ipso C=O not observed); minor diastereoisomer: 19.3 (q), 45.8

(dt, J_{PC} 3.6), 54.2 (dd, J_{PC} 3.6), 73.2 (d), 126.2-141.3 (aryl C) (ipso C=O not observed); δ_P (162 MHz, $CDCl_3$) major diastereoisomer: 34.0 (1 P, s); minor diastereoisomer: 30.5 (1 P, s); *m/z* 470 (M^++1, 90%), 408 (19), 364 (30), 334 (28), 230 (90), 201 (84), 105 (100); (found $[M+H]^+$, 470.1890. $C_{29}H_{29}NO_3P$ requires *m/z*, 470.1885).

*Preparation of Diastereomerically Enriched Phosphinamide Diol (**114**).*

Oxidation of alkene (**112**) (100 mg, 0.26 mmol) according to the above general procedure using AD-mix-β[88,89] (360 mg), potassium osmate(VI) dihydrate (ca. 2 mg) and methanesulfonamide (24 mg, 0.26 mmol) in 1:1 *t*-butanol/ water (1.3 cm^3 of each) gave an inseparable 1.6:1 mixture of diastereomeric diols (**114**) as a viscous oil (99 mg, 91%), υ_{max} (film)/ cm^{-1} 3216, 1718, 1590, 1453, 1438, 1179, 1122, 1027, 997, 851, 727 and 698; δ_H (270 MHz, $CDCl_3$) major diastereoisomer: 0.81 (3 H, s, C*H*$_3$), 0.82 (3 H, s, C*H*$_3$), 1.57 (3 H, d, J 6.9, CHC*H*$_3$), 2.38 (1 H, br s, OH), 2.58 (1 H, br d, J 9.7, C*H*), 3.03-3.15 (1 H, m, C*H*$_2$), 3.27 (1 H, m, C*H*$_2$), 4.51 (1 H, m, C*H*CH_3), 5.77 (1 H, br s, OH), 7.25-7.52 (11 H, m, aryl H), 7.74-7.85 (4 H, m, aryl H); minor diastereoisomer: 0.91 (3 H, s, C*H*$_3$), 1.06 (3 H, s, C*H*$_3$), 1.61 (3 H, d, J 7.1, CHC*H*$_3$), 2.62 (1 H, br s, OH), 3.04-3.11 (1 H, m, C*H*$_2$), 3.11 (1 H, m, C*H*$_2$), 3.68 (1 H, br d, J 9.5, C*H*), 4.47 (1 H, m, C*H*CH_3), 5.93 (1 H, m, OH), 7.25-7.72 (11 H, m, aryl H), 7.83-7.97 (4 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) major diastereoisomer: 17.5 (q), 24.1 (q), 25.8 (q), 46.0 (t), 55.0 (dd, J_{PC} 5.5), 71.3 (s), 74.9 (d), 127.6-141.3 (aryl C); minor diastereoisomer: 20.7 (q), 23.8 (q), 26.2 (q), 46.3 (t), 55.9 (dd, J_{PC} 5.5), 71.7 (s), 76.5 (d), 127.6-141.3 (aryl C); δ_P (162 MHz, $CDCl_3$) major diastereoisomer: 34.6 (1 P, s); minor diastereoisomer: 36.0 (1 P, s); *m/z* (CI) 424 (M^++1, 64%), 406 (14), 390 (30), 364 (38), 230 (100), 201 (75), 105 (50); (found $[M+H]^+$, 424.2042. $C_{25}H_{31}NO_3P$ requires *m/z*, 424.2041).

4.6.3.2 Synthesis of Diastereomerically Pure Phosphinamide Diols (107) and (130) *via* Ring Opening of *t*-BDMS Protected Glycidol.

Preparation of t-BDMS protected glycidol.

To a stirred solution of R-(+)-glycidol (1.79 cm^3, 27 mmol) and triethylamine (4.5 cm^3, 32.4 mmol) in DCM (40 cm^3) was added *t*-butyldimethylsilyl chloride (4.48 g, 29.7 mmol) and DMAP (160 mg, 1.35 mmol). The cloudy solution was stirred at room temperature for 18 hours. Saturated aqueous ammonium chloride solution (15 cm^3) was then added and the mixture extracted with DCM (3 x 10 cm^3). The combined extracts were dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on silica eluting with 0→7% v/v ethyl acetate- petrol to afford the *t*-BDMS protected alcohol as a colourless oil (3.76 g, 73%), $[\alpha]_D^{18}$= +10.1 (*c* 1.92, benzene) (lit.,[94] $[\alpha]_D^{19}$= +4.95 (*c* 1.94, benzene)); δ_H (270 MHz, $CDCl_3$) 0.08 (6 H, s, C*H*$_3$), 0.91 (9 H, s, CMe_3), 2.62 (1 H, dd, J 5.2 and 2.6, C*H*$_2$), 2.78 (1 H, dd, J 4.8 and 4.2, C*H*$_2$), 3.03 (1 H, m, C*H*), 3.66 (1 H, dd, J 12 and 4.6, C*H*$_2$), 3.84 (1 H, dd, J 12 and 3, C*H*$_2$); δ_C (68 MHz, $CDCl_3$) -5.4 (q), 18.3 (s), 25.85 (q), 44.4 (t), 52.4 (d), 63.7 (t).

Preparation of Mono Protected Amino Diol (118).

To a solution of S-3-[(*tert*-Butyldimethylsilyl)oxy]-1, 2-epoxypropane (prepared as described above) (3.7 g, 19.7 mmol) in dry acetonitrile (10 cm^3) was added lithium perchlorate (2.1 g, 19.7 mmol). The mixture was stirred until the lithium salt had dissolved then R-(+)-α methylbenzylamine (2.53 cm^3, 19.7 mmol) was added dropwise and the mixture stirred at room temperature for 12 hours. Water (5 cm^3) was then added and the mixture extracted with ethyl acetate (3 x 5 cm^3). The combined extracts were dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on silica eluting with 0→10% v/v methanol- DCM

to afford the R, S-mono protected amino diol (**118**) (5.48 g, 90%) as a single regioisomer which was further purified by distillation under reduced pressure b. p. 149-153 °C (0.3 mmHg), $[\alpha]_D^{17}$= +16.3 (*c* 0.8, chloroform); υ_{max} (film)/ cm^{-1} 3463, 3291, 3064, 2955, 1603, 1471, 1462, 1361, 1112, 838 and 778, 624; δ_H (270 MHz, $CDCl_3$) 0.01 (6 H, s, C*H*$_3$), 0.85 (9 H, s, CMe$_3$), 1.53 (3 H, d, J 6.6, CHC*H*$_3$), 2.64 (1 H, dd, J 12.1 and 3.7, C*H*$_2$), 2.76 (1 H, dd, J 12 and 8.4, C*H*$_2$), 3.45-3.61 (2 H, m, C*H*$_2$), 3.55 (2 H, br s, OH and NH), 3.71 (1 H, m, C*H*OH), 4.01 (1 H, q, J 7.1, C*H*CH$_3$) 7.26-7.38 (5 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) -5.5 (q), -5.4 (q), 18.2 (s), 22.4 (q), 25.8 (q), 49.8 (t), 59.3 (d), 65.3 (t), 69.65 (d), 126.9 (d), 128.1 (d), 128.9 (d), 141.4 (s); *m/z* (CI) 310 (M^++1, 52%), 294 (18), 252 (19), 148 (28), 134 (53), 120 (33), 105 (100); (found $[M+H]^+$, 310.2202. $C_{17}H_{32}NO_2Si$ requires *m/z*, 310.2202).

Mono Protected Amino Diol (128).

This was prepared according to the above method using (S)-3-[(*tert*-Butyldimethylsilyl)oxy]-1, 2-epoxypropane (prepared as described above) (3.45 g, 18 mmol), lithium perchlorate (1.92 g, 18 mmol) and S-(-)-α methylbenzylamine (2.31 cm^3, 18 mmol) in dry acetonitrile (10 cm^3). The S, S-mono protected amino diol (**128**) (5.34 g, 96%) was isolated as a single regioisomer which was further purified by distillation under reduced pressure, b. p. 150-157 °C (0.4 mmHg), $[\alpha]_D^{20}$= -30.3 (*c* 0.94, chloroform); υ_{max} (film)/ cm^{-1} 3460, 3064, 2928, 1604, 1462, 1389, 1361, 1256, 1108, 837, 777, 701 and 671; δ_H (400 MHz, $CDCl_3$) 0.01 (6 H, s, C*H*$_3$), 0.82 (9 H, s, CMe$_3$), 1.47 (3 H, d, J 6.7, CHC*H*$_3$), 2.51 (1 H, dd, J 12.1 and 8.3, C*H*$_2$), 2.75 (1 H, dd, J 12.2 and 3.4, C*H*$_2$), 3.53 (2 H, br d, J 4.6, C*H*$_2$), 3.81-3.84 (1 H, m, C*H*), 3.82-3.97 (3 H, br m, C*H*CH$_3$, OH and NH), 7.26-7.35 (5 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) -5.5 (q), -5.4 (q), 18.1 (s), 22.7 (q), 25.7 (q), 49.5 (t), 58.5 (d), 65.4 (t), 69.1 (d), 126.7 (d), 127.8 (d), 128.8 (d), 143.7 (s); *m/z* (CI) 310 (M^++1, 100%), 294 (14), 252 (20), 206 (19), 148 (21), 134 (42), 120 (29), 105 (78),

91 (16); (found $[M+H]^+$, 310.2202. $C_{17}H_{32}NO_3P$ requires *m/z*, 310.2202).

Preparation of Epimeric Oxazaphospholidines (124) and (125).

To a stirred solution of R, S-mono protected amino diol (**118**) (5.27 g, 17.06 mmol) and triethylamine (5.22 cm^3, 37.53 mmol) in DCM (150 cm^3) at 0 °C was added phenylphosphonic dichloride (2.41 cm^3, 17.1 mmol) dropwise over 10 minutes. The resulting solution was stirred for 3 hours then warmed to room temperature and stirred for a further 18 hours. Saturated aqueous ammonium chloride solution (50 cm^3) was then added and the mixture extracted with DCM (3 x 30 cm^3). The combined extracts were washed with water (20 cm^3) then saturated aqueous brine (20 cm^3) and dried (magnesium sulfate). The solution was then concentrated *in vacuo* to give a colourless oil consisting of a 1.4:1 mixture of epimeric oxazaphospholidines (**124**) and (**125**) which were readily separated by chromatography on silica, eluting with 0→30% v/v ethyl acetate- petrol. The absolute configuration at phosphorus for the pure epimers was not determined.

Major diastereoisomer: obtained as a colourless oil(1.85 g, 25%), R_f 0.78 (50% ethyl acetate- petrol); $[\alpha]_D^{23}$= +34.1 (*c* 0.41, chloroform); υ_{max} (film)/ cm^{-1} 3060, 2953, 1251, 1132, 837 and 696; δ_H (270 MHz, $CDCl_3$) -0.05 (3 H, s, C*H*3), -0.03 (3 H, s, C*H*3), 0.78 (9 H, s, CMe3), 1.37 (3 H, d, J 6.8, CHC*H*3), 2.97-3.06 (1 H, m, C*H*2), 3.23 (1 H, ddd, J 12.3, 8.1 and 7, C*H*2), 3.62 (1 H, dd, J 13 and 7.1, C*H*2), 3.77 (1 H, dd, J 10.5 and 4.95, C*H*2), 4.12-4.47 (2 H, m, C*H* and C*H*CH3), 7.21-7.52 (8 H, m, aryl H), 7.8-7.88 (2 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) -5.8 (q), 18.2 (s), 19.0 (q), 25.8 (q), 46.4 (dt, J_{PC} 12.8), 53.6 (dd, J_{PC} 5.5), 64.2 (dt, J_{PC} 3.7), 76.7 (d), 127.1, 127.5, 128.4, 128.5, 132.1, 132.2, 132.3, 132.6 (s), 141.7 (d, J_{PC} 5.5); δ_P (162 MHz, $CDCl_3$) 31.75 (1 P, s); *m/z* (CI) 432 (M^++1, 100%), 374 (72), 271 (74), 133 (28), 105 (32), 91 (85); (found $[M+H]^+$, 432.2124. $C_{23}H_{35}NO_3SiP$ requires *m/z*, 432.2123).

Minor diastereoisomer: obtained as a colourless oil (1.28 g, 17%), R_f 0.47 (50% ethyl acetate- petrol); $[\alpha]_D^{23}$= +3.3 (*c* 0.27, chloroform); υ_{max} (film)/ cm^{-1} 3061, 2953, 1250, 1132, 836 and 696; δ_H (270 MHz, $CDCl_3$) 0.01 (6 H, s, C*H*$_3$), 0.84 (9 H, s, CMe$_3$), 1.49 (3 H, d, J 7, CHC*H*$_3$), 3.14-3.32 (2 H, m, C*H*$_2$), 3.67 (1 H, ddd, J 11.1, 3.3 and 1.7, C*H*$_2$), 3.87 (1 H, dd, J 11 and 3.6, C*H*$_2$), 4.18 (1 H, p, J 7.1, C*H*), 4.62-4.65 (1 H, m, C*H*CH$_3$), 7.2-7.49 (8 H, m, aryl H), 7.82-7.89 (2 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) -5.9 (q), -5.8 (q), 18.7 (s), 21.2 (q), 26.1 (q), 47.4 (dt, J_{PC} 10.9), 55.2 (dd, J_{PC} 5.5), 63.5 (dt, J_{PC} 7.3), 76.25 (d), 127.0, 127.3, 127.7, 128.5, 128.7, 128.8, 132.3, 132.35, 132.4 (s), 133.1, 133.15, 142.7 (d J_{PC} 3.7); δ_P (162 MHz, $CDCl_3$) 29.5 (1 P, s); *m/z* (CI) 432 (M^++1, 100%), 374 (32), 270 (52), 133 (19), 105 (30); (found $[M+H]^+$, 432.2124. $C_{23}H_{35}NO_3SiP$ requires *m/z*, 432.2123).

Oxazaphospholidines (129).

This was prepared according to the above method using S, S-mono protected amino diol (**128**) (4.94 g, 15.9 mmol), triethylamine (4.87 cm^3, 34.98 mmol) and phenylphosphonic dichloride (2.27 cm^3, 15.9 mmol) in DCM (140 cm^3). Oxazaphospholidines (**129**) were obtained as a 1:1 mixture of epimers which were readily separated by chromatography on silica as detailed above. Again the absolute stereochemistry at phosphorus was not determined.

Less polar diastereoisomer: obtained as a white solid (1.71 g, 25%), m. p. 65-69 °C (d) (from ethyl acetate/ hexane); R_f 0.82 (50% ethyl acetate- petrol); $[\alpha]_D^{20}$= +14.6 (*c* 1.01, chloroform); υ_{max} (nujol)/ cm^{-1} 2954, 2856, 1439, 1251, 1122, 998, 837, 738 and 696; δ_H (400 MHz, $CDCl_3$) 0.04 (6 H, s, C*H*$_3$), 0.85 (9 H, s, CMe$_3$), 1.55 (3 H, d, J 7, CHC*H*$_3$), 3.35-3.42 (2 H, m, C*H*$_2$), 3.75 (1 H, dd, J 11.6 and 7.4, C*H*$_2$), 3.83 (1 H, dd, J 10.2 and 4.2, C*H*$_2$), 4.42 (1 H, dp, J 6.5 and 2.4, C*H*), 4.5-4.54 (1 H, m, C*H*CH$_3$), 7.22-7.39 (4 H, m, aryl H), 7.42-7.52 (4 H, m, aryl H), 7.54-7.82 (2 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) -4.9 (q), 18.5 (s), 20.4 (q), 26.0 (q), 47.2 (dt,

J_{PC} 12.8), 54.7 (dd, J_{PC} 7.3), 64.5 (t), 77.0 (d), 127.2, 127.7, 128.6, 128.7, 130.9 (s), 132.3, 132.35, 132.4, 132.6, 142.2 (d, J_{PC} 3.7); δ_P (162 MHz, $CDCl_3$) 31.1 (1 P, s); *m/z* (CI) 432 (M^++1, 22%), 374 (28), 133 (56), 115 (20), 89 (54), 75 (100); (found $[M+H]^+$, 432.2124. $C_{23}H_{35}NO_3SiP$ requires *m/z*, 432.2123).

More polar diastereoisomer: obtained as a colourless oil (1.72 g, 25%), R_f 0.55 (50% ethyl acetate- petrol); $[\alpha]_D^{20}$= -31.0 (*c* 3.01, chloroform); υ_{max} (film)/ cm^{-1} 3060, 2929, 1439, 1251, 1131, 837 and 696; δ_H (400 MHz, $CDCl_3$) -0.01 (6 H, s, CH_3), 0.84 (9 H, s, CMe_3), 1.31 (3 H, d, J 7, $CHCH_3$), 2.98 (1 H, ddd, J 10, 11 and 7, CH_2), 3.32 (1 H, dt, J 8.4 and 5.5, CH_2), 3.66 (1 H, dd, J 11.4 and 0.9, CH_2), 3.86 (1 H, dd, J 11 and 3.8, CH_2), 4.44 (1 H, p, J 6.4, CH), 4.56-4.61 (1 H, m, $CHCH_3$), 7.17-7.46 (8 H, m, aryl H), 7.81-7.94 (2 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) -5.05 (q), 14.1 (s), 18.3 (q), 25.7 (q), 45.3 (dt, J_{PC} 9.1), 52.9 (dd, J_{PC} 7.3), 63.3 (dt, J_{PC} 5.5), 75.8 (d), 126.9, 127.3, 128.1, 128.2, 128.3, 130.3 (s), 132.0, 132.6, 132.7, 141.6 (d, J_{PC} 3.6); δ_P (162 MHz, $CDCl_3$) 30.0 (1 P, s); *m/z* (CI) 432 (M^++1, 100%), 374 (26), 328 (14), 270 (70), 133 (20), 40 (44); (found $[M+H]^+$, 432.2124. $C_{23}H_{35}NO_3SiP$ requires *m/z*, 432.2123).

Preparation of R, S-N-phosphinylated Amino Alcohol (126).

Reaction of either epimeric oxazaphospholidine (**124**) or (**125**) with phenylmagnesium bromide gave the R, S-N-phosphinylated amino alcohol (**126**). The following procedure refers to the ring opening of the major oxazaphospholidine product and is typical.

To a stirred solution of the oxazaphospholidine (1.75 g, 4.06 mmol) in anhydrous THF (20 cm^3) at -30 °C was added phenylmagnesium bromide (1 M THF solution, 6.11 cm^3, 6.11 mmol) dropwise over 5 minutes. The mixture was stirred for 1 hour then warmed to room temperature and stirred for a further 18 hours. Water (8 cm^3) was then added and the mixture extracted with DCM (4 x 10 cm^3) [CARE!: emulsification may occur on work up if the mixture is shaken

vigorously]. The combined extracts were dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on silica eluting with 20→40% ethyl acetate- petrol to afford R, S-N-phosphinylated amino alcohol (**126**) as a colourless oil (1.34 g, 65%) $[\alpha]_D^{17}$= +4.1 (*c* 0.29, chloroform); υ_{max} (film)/ cm^{-1} 3314, 3060, 2927, 1471, 1439, 1253, 1119, 910, 836, 730 and 698; δ_H (270 MHz, $CDCl_3$) -0.06 (6 H, s, C*H*$_3$), 0.78 (9 H, s, CMe$_3$), 1.58 (3 H, d, J 7.1, CHC*H*$_3$), 2.81 (1 H, ddd, J 16.2, 10.8 and 3.8, C*H*$_2$), 3.12 (1 H, dd, J 9.7 and 9, C*H*$_2$), 3.38 (1 H, m, C*H*$_2$), 3.61 (1 H, dd, J 10 and 4.2, C*H*$_2$), 3.89 (1 H, m, C*H*OH), 4.41 (1 H, dq, J 8.1 and 7.5, C*H*CH$_3$), 5.78 (1 H, br d, J 2, OH), 7.25-7.48 (11 H, m, aryl H), 7.71-7.88 (4 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) -5.5 (q), 18.2 (s), 20.6 (q), 25.8 (q), 48.7 (t), 56.0 (dd, J_{PC} 5.5), 65.3 (t), 71.95 (d), 127.5, 127.9, 128.4, 128.6, 128.7, 128.8, 128.85, 130.1 (s), 131.4 (s), 131.9, 132.2, 132.25, 132.3, 132.9, 133.0, 140.7 (d, J_{PC} 5.5); δ_P (162 MHz, $CDCl_3$) 36.0 (1 P, s); *m/z* (CI) 510 (M^++1, 52%), 452 (78), 406 (70), 230 (100), 201 (72), 105 (75), 91 (55); (found $[M+H]^+$, 510.2590. $C_{29}H_{41}NO_3SiP$ requires *m/z*, 510.2593).

Repeating the reaction using the minor oxazaphospholidine epimer (1.2 g, 2.78 mmol) and phenylmagnesium bromide (1 M THF solution, 4.17 cm^3, 4.17 mmol) in THF (15 cm^3) gave R, S-N-phosphinylated amino alcohol (**126**) as above (1.06 g, 75%).

S, S-N-phosphinylated Amino Alcohol (130).

This compound was prepared according to the above procedure using oxazaphospholidene (**129**). Both epimers gave S, S-N-phosphinylated amino alcohol (**130**) in identical yield. Treatment of the oxazaphospholidine (1.2 g, 2.78 mmol) with phenylmagnesium bromide (1 M THF solution, 4.17 cm^3, 4.17 mmol) in anhydrous THF (15 cm^3) gave S, S-N-phosphinylated amino alcohol (**130**) as a colourless oil (840 mg, 59%), $[\alpha]_D^{19}$= -78.0 (*c* 0.83, chloroform); υ_{max} (film)/ cm^{-1} 3328, 3060, 2954, 2856, 1438, 1174, 1120, 837, 732 and 698; δ_H (270 MHz,

$CDCl_3$) -0.01 (6 H, s, CH_3), 0.91 (9 H, s, CMe3), 1.71 (3 H, d, J 7, $CHCH_3$), 2.99-3.04 (2 H, m, CH_2), 3.16-3.18 (1 H, m, CH_2), 3.41-3.58 (2 H, m, CHOHand CH_2), 4.63 (1 H, dq, J 10.4 and 7, $CHCH_3$), 5.34 (1 H, br s, OH), 7.33-7.63 (11 H, m, aryl H), 8.0-8.07 (4 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) -5.7 (q), -5.5 (q), 17.6 (s), 17.7 (q), 25.8 (q), 48.1 (dt, J_{PC} 4.4), 54.8 (dd, J_{PC} 4.4), 65.1 (t), 69.3 (d), 127.6, 128.3, 128.6, 128.65, 128.7, 128.8, 131.8, 131.8 (s), 132.0 (s), 132.15, 132.2, 132.35, 132.6, 132.8, 141.7 (d, J_{PC} 3.3); δ_P (162 MHz, $CDCl_3$) 34.9 (1 P, s); *m/z* (CI) 510 (M^++1, 20%), 406 (22), 335 (18), 230 (100), 201 (35), 105 (52); (found $[M+H]^+$, 510.2590. $C_{29}H_{41}NO_3SiP$ requires *m/z*, 510.2593).

Preparation of R, S-Phosphinamide Diol (107).

To a stirred solution of R, S-N-phosphinylated amino alcohol (**126**) (1.18 g, 2.31 mmol) in THF (15 cm^3) at 0 °C was added TBAF (1.1 M THF solution, 4.22 cm^3, 4.64 mmol) dropwise. The resulting pale yellow solution was warmed slowly to room temperature and stirred for 45 minutes. Water (10 cm^3) was then added and the mixture extracted with DCM (3 x 5 cm^3). The combined extracts were dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on silica eluting with 0→5% v/v methanol- DCM to afford R, S-phosphinamide diol (**107**) as a white foam which was further purified by recrystallisation from diethyl ether/ pentane (776 mg, 85%), m. p. 59-61 °C (from diethyl ether/ pentane); $[\alpha]_D^{16}$= +27.1 (*c* 0.58, chloroform); υ_{max} (nujol)/ cm^{-1} 3345, 3059, 2930, 1439, 1381, 1122, 1069, 998, 890, 733 and 697; δ_H (270 MHz, $CDCl_3$) 1.61 (3 H, d, J 7.1, $CHCH_3$), 2.64 (1 H, br t, J 6.4, OH), 2.98-3.09 (2 H, m, CH_2), 3.25-3.42 (2 H, m, CH_2), 3.63-3.71 (1 H, m, CHOH), 4.45 (1 H, m, $CHCH_3$), 5.39 (1 H, d, J 3.3, OH), 7.25-7.38 (5 H, m, aryl H), 7.46-7.55 (6 H, m, aryl H), 7.78-7.91 (4 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 19.9 (q), 47.1 (t), 55.5 (dd, J_{PC} 5.5), 64.0 (t), 70.9 (d), 127.6, 128.5, 128.6, 128.8, 129.6 (d, J_{PC} 4.3), 131.5 (s), 132.0, 132.2, 132.3, 132.5, 132.7, 140.5 (d, J 5.5); δ_P (162 MHz, $CDCl_3$) 36.55 (1 P, s); *m/z* (CI) 396 (M^++1, 66%),

378 (40), 292 (89), 230 (90), 201 (69), 105 (95), 91 (80); (found $[M+H]^+$, 396.1729. $C_{23}H_{27}NO_3P$ requires *m/z*, 396.1728).

S, S-Phosphinamide Diol (127).

This compound was prepared according to the above procedure using S, S-N-phosphinylated amino alcohol (**130**) (0.5 g, 0.98 mmol) and TBAF (1.1 M THF solution, 1.78 cm^3, 1.96 mmol) in THF (7 cm^3). S, S-phosphinamide diol (**127**) was obtained as a white foam which purified by recrystallisation from diethyl ether/ pentane (352 mg, 91%), $[\alpha]_D^{19}$= -113.7 (*c* 0.86, chloroform); υ_{max} (nujol)/ cm^{-1} 3355, 2933, 1438, 1380, 1121, 1072, 997, 888, 733 and 697; δ_H (400 MHz, $CDCl_3$) 1.65 (3 H, d, J 7, $CHCH_3$), 2.81 (1 H, br s, OH), 3.01-3.2 (3 H, m, CH_2), 3.21-3.32 (2 H, m, CH_2 and CHOH), 4.56-4.62 (1 H, m, $CHCH_3$), 5.48 (1 H, br s, OH), 7.35-7.38 (5 H, m, aryl H), 7.41-7.64 (6 H, m, aryl H), 7.93-8.04 (4 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) 18.0 (q), 47.1 (dt, J_{PC} 3.6), 55.0 (dd, J_{PC} 3.6), 64.0 (t), 69.7 (d), 127.6, 128.4, 128.6, 128.7, 128.75, 128.8, 130 (d, J_{PC} 20), 131.2 (d, J_{PC} 20), 132.0, 132.1, 132.2, 132.4, 132.5, 141.1 (d, J_{PC} 3.6); δ_P (162 MHz, CDC_3) 34.4 (1 P, s); *m/z* (CI) 396 (M^++1, 7%), 292 (10), 230 (10), 186 (53), 142 (100), 100 (33); (found $[M+H]^+$, 396.1729. $C_{23}H_{27}NO_3P$ requires *m/z*, 396.1728).

Reaction of Mono Protected Amino Diol (118) with Diphenylphosphinic chloride.

Preparation of O-diphenylphosphinoylated Amino Alcohol (119).

To a stirred solution of mono protected amino diol (**118**) (500 mg, 1.62 mmol) and triethylamine (0.45 cm^3, 3.24 mmol) in DCM (10 cm^3) at 0 °C was added diphenylphosphinic chloride (0.31 cm^3, 1.62 mmol) dropwise. The solution was stirred for 6 hours. Saturated aqueous ammonium chloride solution (5 cm^3)

was then added and the mixture extracted with DCM (3 x 5 cm^3). The combined extracts were washed with saturated aqueous brine (5 cm^3), dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on silica eluting with 0→10% v/v methanol- DCM to afford O-diphenylphosphinoylated amino alcohol (**119**) as a pale yellow oil (392 mg, 48%), υ_{max} (film)/ cm^{-1} 3300, 2955, 2856, 1439, 1228, 1130, 1036, 978, 837 and 699; δ_H (270 MHz, $CDCl_3$) 0.01 (6 H, s, CH_3), 0.86 (9 H, s, CMe_3), 1.32 (3 H, d, J 6.6, $CHCH_3$), 2.25 (1 H, br m, NH), 2.71-2.82 (2 H, m, CH_2), 3.69-3.77 (3 H, m, CH_2 and CH), 4.41-4.49 (1 H, m, $CHCH_3$), 7.29-7.81 (11 H, m, aryl H), 7.82-7.92 (4 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) -5.6 (q), 18.1 (q), 24.3 (s), 25.8 (q), 48.8 (dt, J_{PC} 2.2), 57.6 (d), 64.1 (dt, J_{PC} 11.1), 76.2 (d), 126.6, 126.85, 128.3, 128.4, 128.5, 131.5, 131.6, 131.7, 131.9, 132.0, 132.1; δ_P (162 MHz, $CDCl_3$) 32.2 (1 P, s); *m/z* (CI) 510 (M^+, 78%), 452 (14), 333 (36), 233 (100), 201 (22), 155 (32), 105 (46), 91 (27); (found $[M+H]^+$, 510.2590. $C_{29}H_{41}NO_3SiP$ requires *m/z*, 510.2593).

Reaction of Mono Protected Amino Diol (118) with *t*-Butyldimethylsilyl chloride.

Preparation of N-t-BDMS Protected Amino Alcohol (120).

To a stirred solution of mono protected amino diol (**118**) (200 mg, 0.647 mmol) and triethylamine (0.11 cm^3, 0.78 mmol) in DCM (1 cm^3) was added *t*-butyldimethylsilyl chloride (107 mg, 0.71 mmol) and DMAP (5 mg, 0.03 mmol). The cloudy solution was stirred at room temperature for 18 hours. Saturated aqueous ammonium chloride solution (0.5 cm^3) was then added and the mixture extracted with DCM (3 x 1 cm^3). The combined extracts were then dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on silica eluting with 0→5% v/v ethyl acetate- petrol to afford N-*t*-BDMS protected amino alcohol (**120**) as a colourless oil (153 mg, 56%), (found C, 65.2; H, 10.9; N, 3.4.

$C_{23}H_{45}NO_2Si_2$ requires C, 65.19; H, 10.64; N, 3.31%); υ_{max} (film)/ cm^{-1} 2955, 2885, 1463, 1255, 1101, 1005, 836, 776 and 700; δ_H (270 MHz, $CDCl_3$) 0.06 (6 H, s, CH_3), 0.07 (6 H, s, CH_3), 0.88 (18 H, s, CMe_3), 1.34 (3 H, d, J 7, $CHCH_3$), 1.66 (1 H, br s, OH), 2.43-2.55 (2 H, m, CH_2), 3.46-3.58 (2 H, m, CH_2), 3.67-3.81 (2 H, m, $CHCH_3$ and CHOH), 7.26-7.31 (5 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) -4.7 (q), -4.3 (q), 18.1 (s), 18.3 (s), 24.6 (q), 25.9 (q), 51.2 (t), 58.2 (d), 66.1 (t), 72.6 (d), 126.6 (d), 126.7 (d), 128.3 (d), 145.9 (s); *m/z* (CI) 424 (M^++1, 24%), 408 (22), 366 (40), 291 (26), 134 (62), 120 (36), 105 (100).

Reduction of Acetophenone with BMS Catalysed by the Boronate Complexes of the Phosphinamide Diols.

The boronate complexes of the appropriate phosphinamide diol were generated *in situ* by reaction of a THF solution of the phosphinamide diol with BMS as described below. The presence of impurities, particularly water, appeared to have a detrimental effect on catalyst performance. The phosphinamide diol was doubly recrystallised from diethyl ether/ pentane and dried *via* azeotropic removal of water using chloroform. The ketone (initially purified and dried by distillation from calcium hydride) was dissolved in anhydrous THF (2 M solution) and dried for 18 hours over activated 4Å molecular sieves prior to use. The following procedure is typical.

Reduction Catalysed by Boronate (108).

To a stirred solution of phosphinamide diol (**107**) (50 mg, 0.127 mmol) in anhydrous THF (0.5 cm^3) was added BMS (10 M dimethyl sulfide complex, 0.014 cm^3, 0.14 mmol) dropwise. The solution was stirred for 2 hours at room temperature. Acetophenone (2 M THF solution, 0.63 cm^3, 1.27 mmol) was then added followed by BMS (10 M dimethyl sulfide complex, 0.13 cm^3, 1.27 mmol).

The mixture was stirred for 2 hours at room temperature by which time all of the acetophenone had been reduced (by TLC). The solution was then diluted with diethyl ether (5 cm^3) and poured into saturated aqueous ammonium chloride solution (5 cm^3). The mixture was then extracted with diethyl ether (3 x 5 cm^3), the combined extracts dried (magnesium sulfate) and concentrated *in vacuo*. The catalyst was removed by chromatography on silica, eluting with 20% v/v ethyl acetate- petrol, to afford 1-phenylethanol as a colourless oil (136 mg, 88%), 59% e.e. (S- major) as assessed by HPLC analysis (conditions as described in Section 4.1); δ_H (270 MHz, $CDCl_3$) 0.95 (3 H, t, J 7.1, C*H*$_3$), 1.36-1.61 (6 H, m, C*H*$_2$), 5.15 (2 H, s, C*H*Ph), 7.26-7.42 (10 H, m, aryl H).

Section 4.7: Phosphinamide N-protecting Groups for Intramolecular Directed Ketone Reduction.

Oxidation of N-Protected Amino Alcohols.

Preparation of Ketophosphinamide (142).

To a stirred solution of pyridinium dichromate (1.07 g, 2.86 mmol) in DMF (10 cm^3) at 0 °C was added N-diphenylphosphinyl protected 1R, 2S-(-)-norephedrine (**93**) (prepared as described in Section 4.6) (200 mg, 0.57 mmol) portionwise. The mixture was stirred at room temperature for 3 hours. Water (12 cm^3) was then added and the mixture extracted with diethyl ether (3 x 5 cm^3). The combined extracts were washed with water (2 x 5 cm^3) then saturated aqueous brine (8 cm^3) and dried (magnesium sulfate). The diethyl ether solution was filtered through a pad of magnesium sulfate and the filtrate concentrated *in vacuo* to afford ketophosphinamide (**142**) as a pale yellow solid which was further purified by recrystallisation from diethyl ether/ pentane (180 mg, 90%), m. p. 124-127 °C (from diethyl ether/ pentane); $[\alpha]_D^{24} = -1.7$ (*c* 0.88, chloroform); υ_{max} (nujol)/ cm^{-1} 1686, 1178, 935 and 790; δ_H (270 MHz, $CDCl_3$) 1.37 (3 H, d, J 7, CHC*H*$_3$), 4.24 (1 H, br t, J 9.5, NH), 4.88 (1 H, m, C*H*CH_3), 7.29-7.52 (9 H, m, aryl H), 7.72-7.89 (6 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 22.9 (dq, J_{PC} 3.3), 50.9 (d), 128.3, 128.4, 128.5, 128.6, 128.7, 131.2 (s), 131.8, 131.85, 131.9, 132.0, 133.1 (s), 133.6, 133.8 (s), 200.0 (d, J_{PC} 5.5); δ_P (162 MHz, $CDCl_3$) 23.0 (1 P, s); *m/z* (CI) 350 (M^++1, 100%), 244 (40), 218 (19), 201 (14); (found $[M+H]^+$, 350.1321. $C_{21}H_{21}NO_2P$ requires *m/z*, 350.1310).

Preparation of S-2-(N-(tert-butyloxycarbonyl) amino) propiophenone (144).

This compound was prepared according to the above method using *t*-BOC protected amino alcohol (**143**) (prepared as described below) (140 mg, 0.56 mmol) and pyridinium chlorochromate (1.05 g, 2.8 mmol) in DMF (7 cm^3). Chromatography on silica eluting with 0→20% v/v ethyl acetate- petrol afforded ketone (**144**) as a colourless oil which solidified on standing (97 mg, 70%), $[\alpha]_D^{18}$= -3.6 (*c* 2.1, DCM) (lit.,[105a] $[\alpha]_D^{23}$= -3.4 (*c* 2, DCM)); δ_H (270 MHz, $CDCl_3$) 1.41 (3 H, d, J 7.1, $CHCH_3$), 1.45 (9 H, s, CMe_3), 5.29 (1 H, p, J 7.3, $CHCH_3$), 5.55 (1 H, br s, NH), 7.46-7.63 (3 H, m, aryl H), 7.96-7.99 (2 H, m, aryl H); *m/z* (CI) 250 (M^++1, 8%), 194 (100), 150 (58), 105 (13).

Preparation of Ketophosphinamide (148).

To a stirred solution of N-diphenylphosphinyl protected 2-amino-1-phenylethanol (**147**) (prepared as described in Section 4.6) (500 mg, 1.48 mmol) and NMO (312 mg, 2.66 mmol) in DCM (4 cm^3) was added powdered 4Å molecular sieves (20 mg) and TPAP (26 mg, 0.074 mmol). The dark green mixture was stirred at room temperature for 30 minutes then filtered through a pad of silica, eluting with ethyl acetate. The filtrate was concentrated *in vacuo* to afford ketophosphinamide (**148**) as a pale yellow solid which was purified by recrystallisation from ethyl acetate/ petrol (401 mg, 81%), υ_{max} (nujol)/ cm^{-1} 1695, 1448, 1194, 1118, 982, 726 and 696; δ_H (270 MHz, $CDCl_3$) 4.21 (1 H, br m, NH), 4.42 (2 H, dd, J 5.7 and 5.2, CH_2), 7.35-7.51 (9 H, m, aryl H), 7.54-7.88 (6 H, m, aryl H); δ_C (100 MHz, $CDCl_3$) 46.4 (t), 127.7, 128.6, 128.7, 128.8, 131.3, 131.8, 131.9, 132.0, 132.2 (s), 132.6, 133.9, 142.0 (s), 194.6 (d, J_{PC} 9.1); δ_P (162 MHz, $CDCl_3$) 23.7 (1 P, s); *m/z* (CI) 336 (M^++1, 31%), 246 (15), 218 (33), 132 (100), 105 (14), 86 (97); (found $[M+H]^+$, 336.1153. $C_{20}H_{19}NO_2P$ requires *m/z*, 336.1153).

Preparation of Ketophosphinamide (148) Directly from the α-Amino Ketone.

To a stirred solution of diphenylphosphinic chloride (0.60 cm^3, 3.17 mmol) and triethylamine (0.62 cm^3, 4.43 mmol) in DCM (50 cm^3) at 0 °C was added α-aminoacetophenone hydrochloride (362 mg, 2.11 mmol) portionwise over 2 hours [CARE!: rapid addition of the amino ketone results in preferential formation of the dimer product (see Section 2.7)]. The solution was then warmed to room temperature and saturated aqueous ammonium chloride solution added (15 cm^3). The mixture was extracted with DCM (3 x 10 cm^3) and the combined extracts washed with saturated aqueous brine (10 cm^3), dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on silica eluting with 0→5% v/v methanol- DCM to afford ketophosphinamide **(148)** as an off-white solid (636 mg, 90%). The data for this compound is given above.

Reduction of Ketophosphinamide (142).

1) Reduction with BMS.

To a stirred solution of ketophosphinamide **(142)** (prepared as described above) (162 mg, 0.464 mmol) in anhydrous THF (2 cm^3) was added BMS (10 M dimethyl sulfide complex, 0.028 cm^3, 0.28 mmol) dropwise. The mixture was stirred at room temperature for 45 minutes by which time all of the ketone had been reduced (by TLC). The solution was diluted with diethyl ether (5 cm^3) and poured into saturated aqueous ammonium chloride solution (2 cm^3). The mixture was then extracted with diethyl ether (3 x 1 cm^3) and the combined extracts dried (magnesium sulfate) and concentrated *in vacuo* to afford the *syn*-alcohol 1R, 2S-(**93**) as a single diastereoisomer (as assessed by ^1H and ^{31}P NMR data) (148 mg, 92%), δ_H (270 MHz, $CDCl_3$) 1.00 (3 H, d, J 6.8, $CHCH_3$), 3.01-3.09 (1 H, m, NH), 3.32-3.45 (1 H, m, $CHCH_3$), 4.72 (1 H, br d, J 5.9, CHPh), 5.81 (1 H, br d, J 8,

OH), 7.13-7.45 (11 H, m, aryl H), 7.71-7.88 (4 H, m, aryl H); δ_P (162 MHz, $CDCl_3$) 25.05 (1 P, s); (full data for this compound is given in Section 4.6).

2) Reduction with Sodium Borohydride.

To a stirred solution of ketophosphinamide (**142**) (prepared as described above) (100 mg, 0.287 mmol) in 9:1 ethanol/ water (2 cm^3) was added sodium borohydride (5 mg, 0.08 mmol). The solution was stirred for 25 minutes at room temperature after which time all of the ketone had been reduced (by TLC). The mixture was then concentrated *in vacuo* and the residue dissolved in DCM (5 cm^3). The solution was washed with water (2 cm^3) followed by saturated aqueous brine (2 cm^3). It was then dried (magnesium sulfate) and concentrated *in vacuo* to afford alcohol (**93**) as a white solid consisting of an inseparable 2:1 mixture of diastereoisomers (*syn*-alcohol 1R, 2S-(**93**) major) (91 mg, 90%), δ_H (270 MHz, $CDCl_3$) 1R, 2S-diastereoisomer: 0.97 (3 H, d, J 6.4, $CHCH_3$), 3.11-3.18 (1 H, m, NH), 3.36-3.39 (1 H, m, $CHCH_3$), 4.79 (1 H, m, CHPh), 5.93 (1 H, d, J 6.6, OH), 7.11-7.45 (11 H, m, aryl H), 7.71-7.81 (4 H, m, aryl H); 1S, 2S-diastereoisomer: 1.05 (3 H, d, J 6.6, $CHCH_3$), 3.22-3.28 (1 H, m, NH), 3.35-3.44 (1 H, m, $CHCH_3$), 4.44 (1 H, br s, CHPh), 5.61 (1 H, br s, OH), 7.07-7.45 (11 H, m, aryl H), 7.71-7.83 (4 H, m, aryl H).

Preparation of t-BOC Protected Norephedrine (143).

To a stirred solution of 1R, 2S-(-)-norephedrine (100 mg, 0.66 mmol) and triethylamine (0.10 cm^3, 0.727 mmol) in DCM (15 cm^3) was added di-*t*-butyl dicarbonate (144 mg, 0.66 mmol) portionwise. The solution was stirred at room temperature for 18 hours then poured into saturated aqueous ammonium chloride solution (8 cm^3). The mixture was extracted with DCM (3 x 5 cm^3) and the combined extracts dried (magnesium sulfate) and concentrated *in vacuo* to afford

the protected amino alcohol (**143**) as a viscous oil (142 mg, 86%), $[\alpha]_D^{20} = -18.5$ (*c* 0.05, chloroform); δ_H (270 MHz, $CDCl_3$) 0.91 (3 H, d, J 7, $CHCH_3$), 1.39 (9 H, s, CMe_3), 3.36 (1 H, br m, NH), 3.91-3.93 (1 H, m, $CHCH_3$), 4.62 (1 H, br d, J 3.8, CHPh), 4.77 (1 H, br s, OH), 7.23-7.28 (5 H, m, aryl H).

Reduction of *t*-BOC Protected Amino Ketone (144) with BMS.

To a stirred solution of ketone (**144**) (87 mg, 0.35 mmol) in anhydrous THF (1 cm^3) was added BMS (10 M dimethyl sulfide complex, 0.02 cm^3, 0.21 mmol) dropwise. The solution was stirred at room temperature for 18 hours. The mixture was then diluted with diethyl ether (5 cm^3), poured into saturated aqueous ammonium chloride solution (2 cm^3) and extracted with diethyl ether (3 x 2 cm^3). The combined extracts were dried (magnesium sulfate) and concentrated *in vacuo* to afford the alcohol as an inseparable 3.75:1 mixture of diastereoisomers (*syn*-alcohol 1R, 2S-(**143**) major) (61 mg, 70%), δ_H (400 MHz, $CDCl_3$) 1R, 2S-diastereoisomer: 0.96 (3 H, d, J 7, $CHCH_3$), 1.45 (9 H, s, CMe_3), 3.52 (1 H, br m, NH), 3.95 (1 H, br m, $CHCH_3$), 4.62-4.67 (1 H, m, CHPh), 4.83 (1 H, br s, OH), 7.25-7.33 (5 H, m, aryl H); 1S, 2S-diastereoisomer: 1.05 (3 H, d, J 6.7, $CHCH_3$), 1.43 (9 H, s, CMe_3), 3.51-3.53 (1 H, br m, NH), 3.84 (1 H, br m, $CHCH_3$), 4.75-4.77 (1 H, m, CHPh), 4.85 (1 H, br s, OH), 7.25-7.39 (5 H, m, aryl H).

Reduction of Ketophosphinamide (148) with BMS in the Presence of Boronate (98).

To a stirred solution of R, R-(-)-butanediol (**97**, R=Me) (4.1 mg, 0.045 mmol) in THF (1.5 cm^3) was added BMS (10 M dimethyl sulfide complex, 5 µl, 0.054 mmol). The solution was stirred at room temperature for 20 minutes then ketone (**148**) (150 mg, 0.45 mmol) was added followed by BMS (10 M dimethyl sulfide solution, 0.027 cm^3, 0.27 mmol) dropwise. The resulting mixture was then

stirred at room temperature for 30 minutes by which time all of the ketone had been reduced (by TLC). The solution was diluted with diethyl ether, poured into saturated aqueous ammonium chloride solution (1 cm^3) and extracted with diethyl ether (3 x 1 cm^3). The combined extracts were dried (magnesium sulfate) and concentrated *in vacuo* to afford alcohol (**147**) as a white solid (128 mg, 85%), δ_H (270 MHz, $CDCl_3$) 3.08-3.82 (2 H, m, CH_2), 3.82 (1 H, br m, NH), 4.85-4.87 (1 H, m, C*H*Ph), 7.23-7.45 (12 H, m, aryl H and OH), 7.75-7.86 (4 H, m, aryl H); (full data for the racemic alcohol is given in Section 4.6).

Determination of Enanteomeric Purity by Formation of Moshers Esters.

The method is based on a literature procedure.[114] To a stirred solution of the above alcohol (50 mg, 0.15 mmol) in DCM (1 cm^3) was added DMAP (2 mg, 0.015 mmol) and R-(+)-α methoxy-α-(trifluoromethyl) phenylacetic acid (52 mg, 0.22 mmol). The solution was cooled to 0 °C and DCC (46 mg, 0.22 mmol) added portionwise. The resulting mixture was then allowed to warm to room temperature and stirred for 18 hours by which time all of the alcohol was consumed (by TLC). The precipitated DCU was then filtered off and the filtrate washed rapidly with cold 0.5 M HCl (0.5 cm^3) followed by saturated aqueous sodium bicarbonate solution (0.5 cm^3). The solution was dried (magnesium sulfate) and concentrated *in vacuo* to afford a mixture of MTPA-esters as a colourless oil (81 mg, 97%). ^{31}P NMR analysis of the crude mixture indicated a 3% diastereomeric excess, δ_P (162 MHz, $CDCl_3$) major diastereoisomer: 24.1 (1 P, s); minor diastereoisomer: 24.2 (1 P, s).

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6 Appendix.

Single Crystal X-Ray Study of Phosphinamide (**29**).

A Crystal of approximate dimensions 0.3 x 0.2 x 0.2 mm was used for data collection.

Crystal data: $C_{20}H_{20}NOP$, M=321.3 tetragonal, a = 11.475(3), b = 11.475(3), c = 13.328(7) Å, U=1755.0 Å, space group $P4_1$, Z = 4, D_c = 1.22 gcm^{-3}, μ(Mo-K_α) = 1.50 cm^{-1}, F(000) = 680. Data were measured at room temperature on a Hilger and Watts Y290 four-circle diffractometer in the range $2 \leq \theta \leq 24^o$. 3048 reflections were collected of which 844 were unique with $I \geq 3\sigma(I)$. Data were collected for Lorentz and polarization effects but not for absorption. The structure was solved by Patterson methods and refined using the SHELX[1,2] suite of programs. In the final least squares cycles all atoms were allowed to vibrate anisotropically. Hydrogen atoms were at calculated positions except in the case of H1 which was located in the penultimate Difference Fourier and refined at a distance of 1.08 Å from N1. Final residuals after 10 cycles of least squares were R = 0.0447, R_w = 0.0455, for a weighting scheme of $w = 0.8870/[\sigma^2(F) + 0.003723(F)^2]$. Max. final shift/esd was 0.025. The max. and min. residual densities were 0.09 and -0.06 $eÅ^{-3}$ respectively. Final fractional atomic co-ordinates and isotropic thermal parameters, bond distances and angles are given in Tables A1 to A7 respectively. The asymmetric unit is shown in Figure 10, along with the labelling scheme used.

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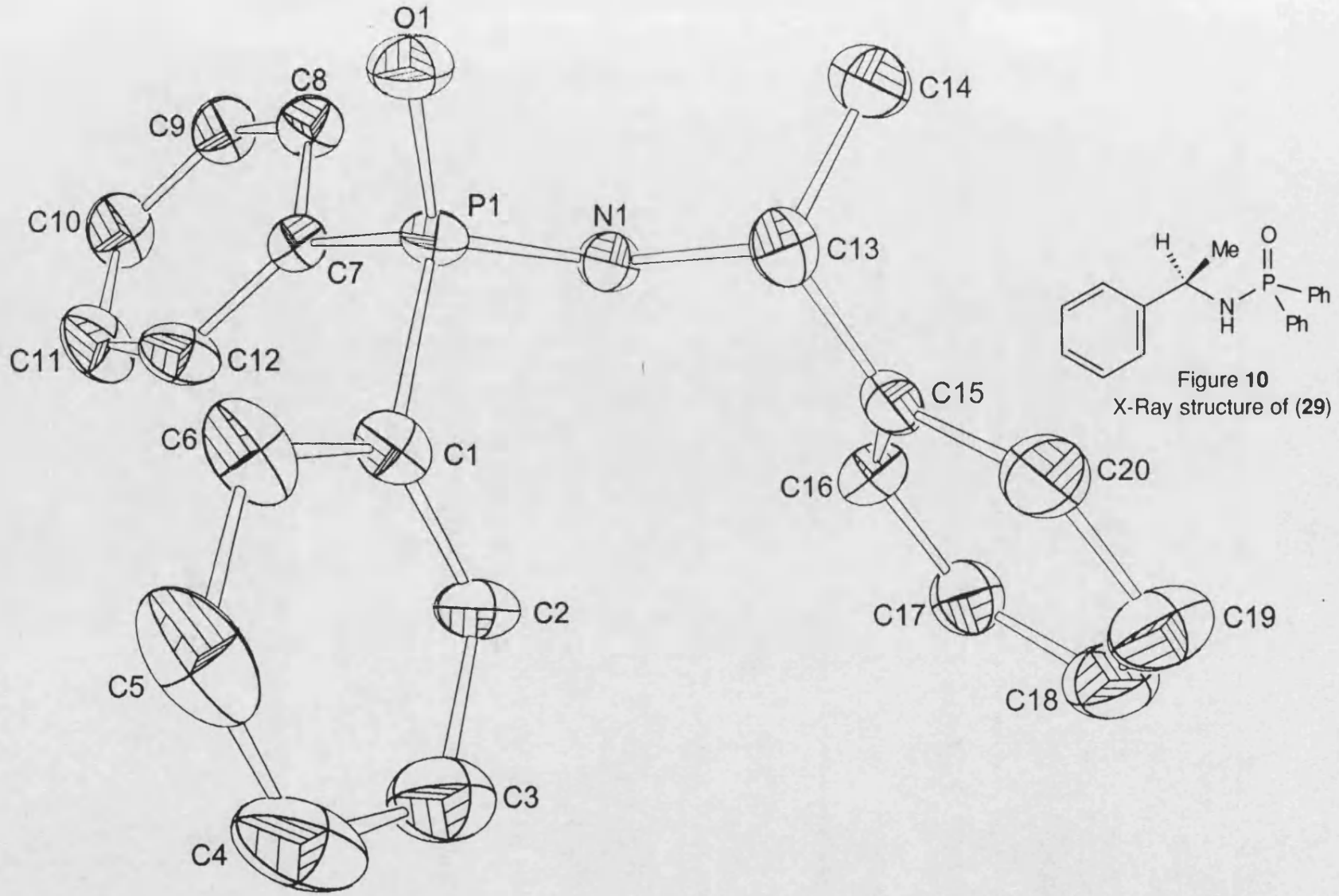

Figure **10**
X-Ray structure of (**29**)

Table A1 Fractional Atomic co-ordinates and thermal parameters (Å) for (**29**)

Atom	X	Y	Z	U
P1	0.22543 (15)	0.87790 (15)	0.19021	0.0429 (11)
O1	0.2313 (4)	1.0001 (4)	0.2271 (5)	0.062 (3)
N1	0.2057 (5)	0.8587 (5)	0.0724 (5)	0.051 (4)
C1	0.3613 (6)	0.8059 (6)	0.2226 (6)	0.050 (5)
C2	0.4039(7)	0.7136 (6)	0.1656 (7)	0.060(5)
C3	0.5048 (9)	0.6586 (9)	0.1932 (11)	0.087 (7)
C4	0.5652 (9)	0.6938 (11)	0.2776 (13)	0.099(9)
C5	0.5231 (9)	0.7860 (12)	0.3336 (10)	0.098 (8)
C6	0.4205 (8)	0.8417 (8)	0.3083 (8)	0.071 (6)
C7	0.1081 (6)	0.7961 (6)	0.2466 (6)	0.045 (4)
C8	-0.0065 (6)	0.8335 (7)	0.2314 (7)	0.058 (5)
C9	-0.0965 (7)	0.7767 (8)	0.2760 (7)	0.071 (6)
C10	-0.0763 (8)	0.6858 (9)	0.3408 (8)	0.081 (7)
C11	0.0342 (8)	0.6458 (9)	0.3548 (9)	0.084 (7)
C12	0.1281 (7)	0.7046 (7)	0.3111 (8)	0.069 (6)
C13	0.2754 (6)	0.9215 (7)	-0.0036 (6)	0.055 (5)
C14	0.1999 (9)	1.0114 (7)	-0.0593 (8)	0.078 (6)
C15	0.3328 (6)	0.8422 (7)	-0.0764 (6)	0.052 (5)
C16	0.2829 (7)	0.7430 (8)	-0.0045 (7)	0.063 (5)
C17	0.3364 (9)	0.6731 (8)	-0.1829 (7)	0.076 (7)
C18	0.4473 (11)	0.7025 (12)	-0.2181 (9)	0.096 (9)
C19	0.5012 (10)	0.8001 (13)	-0.1819 (10)	0.099 (9)
C20	0.4454 (8)	0.8707 (9)	-0.1130 (8)	0.079 (7)
H1	0.1327 (57)	0.8167 (78)	0.0378 (69)	0.107 (8)

Table A2 Fractional Atomic Co-ordinates for the Hydrogen Atoms.

Atom	X	Y	Z
H21	0.3571	0.6855	0.0996
H31	0.5378	0.5877	0.1481
H41	0.6439	0.6493	0.3001
H51	0.5717	0.8151	0.3983
H61	0.3869	0.9117	0.3540
H81	-0.0234	0.9081	0.1841
H91	-0.1848	0.8038	0.2605
H101	-0.1482	0.6456	0.3800
H111	0.0498	0.5692	0.3999
H121	0.2163	0.6786	0.3281
H131	0.3438	0.9663	0.0366
H141	0.2526	1.0568	-0.1138
H142	0.1653	1.0731	-0.0059
H143	0.1289	0.9677	-0.0970
H161	0.1965	0.7196	-0.0893
H171	0.2934	0.5952	-0.2093
H181	0.4898	0.6482	-0.2732
H191	0.5875	0.8225	-0.2081
H201	0.4883	0.9486	-0.0863

Table A3 Anisotropic Thermal Parameters (Å).

Atom	U11	U22	U33	U23	U13	U12
P1	0.040(1)	0.034 (1)	0.054 (1)	-0.001 (1)	-0.003 (1)	0.000 (1)
O1	0.071 (4)	0.037 (3)	0.077 (4)	-0.005 (2)	0.006 (3)	0.004 (2)
N1	0.038 (3)	0.048 (3)	0.066 (5)	0.007 (3)	0.008 (3)	-0.003 (3)
C1	0.039 (4)	0.047 (4)	0.064 (6)	0.013 (4)	-0.005 (4)	-0.008 (3)
C2	0.050 (4)	0.050 (5)	0.079 (7)	0.005 (4)	0.002 (4)	0.013 (4)
C3	0.062 (6)	0.077 (6)	0.123 (10)	0.024 (7)	0.018 (8)	0.014 (5)
C4	0.045 (6)	0.086 (8)	0.165 (13)	0.059 (8)	0.001 (8)	0.006 (6)
C5	0.053 (6)	0.118 (9)	0.122 (10)	0.054 (8)	-0.039 (6)	-0.036 (6)
C6	0.062 (6)	0.072 (6)	0.078 (7)	0.023 (5)	-0.016 (5)	-0.021 (4)
C7	0.040 (4)	0.048 (4)	0.046 (5)	-0.006 (4)	-0.003 (4)	-0.003 (3)
C8	0.036 (4)	0.066 (5)	0.073 (6)	0.001(4)	0.002 (4)	0.003 (4)
C9	0.043 (5)	0.095 (7)	0.076 (7)	0.014 (6)	0.015 (4)	0.006 (5)
C10	0.055 (6)	0.101 (8)	0.087 (7)	0.018 (7)	0.014 (5)	-0.009 (5)
C11	0.072 (6)	0.085 (7)	0.096 (8)	0.047 (6)	0.012 (6)	-0.014 (5)
C12	0.050 (5)	0.058 (5)	0.098 (7)	0.020 (5)	-0.004 (5)	0.004 (5)
C13	0.048 (4)	0.055 (5)	0.062 (5)	0.005 (4)	0.000 (4)	-0.015 (4)
C14	0.084 (6)	0.057 (5)	0.094 (7)	0.011 (6)	0.010 (6)	0.007 (4)
C15	0.052 (4)	0.051 (4)	0.054 (5)	0.014 (4)	0.001 (4)	0.002 (3)
C16	0.060 (5)	0.068 (6)	0.061 (6)	-0.010 (5)	0.010 (4)	0.008 (4)
C17	0.080 (7)	0.088 (7)	0.060 (6)	0.001 (5)	-0.001 (5)	0.012 (5)
C18	0.104 (10)	0.110 (9)	0.073 (8)	-0.007 (7)	0.011 (6)	0.043 (8)
C19	0.068 (6)	0.122 (10)	0.108 (10)	0.005 (8)	0.021 (6)	0.027 (7)
C20	0.048 (5)	0.088 (7)	0.100 (8)	0.018 (6)	0.009 (5)	0.002 (5)

Table A4 Bond Lengths (Å).

P1 - O1	1.487 (5)	**P1 - N1**	1.601 (7)
P1 - C1	1.817 (7)	**P1 - C7**	1.805 (7)
N1 - H1	1.071 (20)	**N1 - C13**	1.479 (10)
C1 - C2	1.392 (11)	**C1 - C6**	1.391 (11)
C2 - C3	1.369 (13)	**C3 - C4**	1.382 (18)
C4 - C5	1.381 (18)	**C5 - C6**	1.382 (14)
C7 - C8	1.398 (10)	**C7 - C12**	1.377 (11)
C8 - C9	1.359 (11)	**C9 - C10**	1.374 (12)
C10 - C11	1.361 (13)	**C11 - C12**	1.398 (11)
C13 - C14	1.538 (11)	**C13 - C15**	1.484 (11)
C15 - C16	1.373 (11)	**C15 - C20**	1.420 (12)
C16 - C17	1.360 (12)	**C17 - C18**	1.398 (15)
C18 - C19	1.367 (16)	**C19 - C20**	1.382 (15)

Table A5 Intermolecular distances (Å).

O1 --- N1	2.87	4	-1.0	1.0	-1.0
O1 --- H1	1.81	4	-1.0	1.0	-1.0
O1 --- H143	2.89	4	-1.0	1.0	-1.0
O1 --- H161	2.49	4	-1.0	1.0	-1.0
H21 --- C18	2.96	4	0.0	1.0	-1.0
H21 --- C19	2.81	4	0.0	1.0	-1.0
C3 --- H121	2.90	3	1.0	0.0	0.0
H31 --- C4	2.98	3	1.0	0.0	0.0
C6 --- H201	2.98	2	1.0	2.0	-1.0
C6 --- H111	2.99	3	1.0	0.0	0.0
H61 --- C9	2.97	4	-1.0	1.0	-1.0
H101 - C18	2.86	3	1.0	1.0	-1.0
C16 - H191	3.00	4	0.0	1.0	-1.0
C17 - H181	3.00	4	0.0	1.0	-1.0

Table A6 Bond Angles (°)

N1 -- P1 -- O1	117.4 (3)	**C1 -- P1 -- O1**	108.2 (3)
C1 -- P1 -- N1	107.0 (4)	**C7 -- P1 -- O1**	112.7 (3)
C7 -- P1 -- N1	103.3 (3)	**C7 -- P1 -- C1**	107.7 (3)
H1 -- N1 -- P1	126 (6)	**C13 -- N1 -- P1**	121.9 (5)
C13 -- N1 -- H1	110 (6)	**C2 -- C1 -- P1**	121.2 (6)
C6 -- C1 -- P1	118.7 (7)	**C6 -- C1 -- C2**	120.1 (8)
C3 -- C2 --C1	120 (1)	**C4 -- C3 --C2**	120 (1)
C5 -- C4 -- C3	119.3 (9)	**C6 -- C5 -- C4**	121 (1)
C5 -- C6 -- C1	119 (1)	**C8 -- C7 -- P1**	118.8 (6)
C12 -- C7 -- P1	122.2 (6)	**C12 -- C7 -- C8**	118.8 (7)
C9 -- C8 -- C7	120.3 (8)	**C10 -- C9 -- C8**	120.7 (8)
C11 -- C10 -- C9	120.0 (9)	**C12 -- C11 -- C10**	119.9 (9)
C11 -- C12 --C7	120.0 (8)	**C14 -- C13 -- N1**	110.6 (7)
C15 -- C13 -- N1	112.9 (6)	**C15 -- C13 --C14**	110.2 (7)
C16 -- C15 -- C13	124.4 (7)	**C20 -- C15 -- C13**	119.2 (8)
C20 -- C15 -- C16	116.3 (8)	**C17 -- C16 -- C15**	123.3 (9)
C18 -- C17 -- C16	120 (1)	**C19 -- C18 -- C17**	119 (1)
C20 -- C19 -- C18	120 (1)	**C19 -- C20 -- C15**	121 (1)

Table A7 Intramolecular Distances (Å).

P1 -- H1	2.40	**P1 -- C2**	2.80
P1 -- H21	2.94	**P1 --C6**	2.77
P1 -- H61	2.89	**P1 -- C8**	2.77
P1 -- H81	2.88	**P1 -- C12**	2.79
P1 -- H121	2.94	**P1 -- C13**	2.69
P1 -- H131	2.66	**O1 -- N1**	2.64
O1 -- C1	2.68	**O1 -- H61**	2.66
O1 -- C7	2.75	**O1 -- H131**	2.87
N1 -- C1	2.75	**N1 -- H21**	2.66
N1 -- C7	2.68	**N1 -- H131**	2.06
N1 -- C14	2.48	**N1 -- H142**	2.71
N1 -- H143	2.73	**N1 -- C15**	2.47
N1 -- C16	2.96	**N1 -- H161**	2.68
H1 -- C7	2.81	**H1 -- C13**	2.11
H1 -- C14	2.69	**H1 -- H143**	2.50
H1 -- C15	2.77	**H1 -- C16**	2.79
H1 -- H161	2.16	**C1 -- H21**	2.15
C1 -- C3	2.39	**C1 -- C4**	2.77
C1 -- C5	2.39	**C1 -- H61**	2.15
C1 -- C7	2.93	**C1 -- H121**	2.62
C2 -- H31	2.12	**C2 -- C4**	2.39
C2 -- C5	2.75	**C2 -- C6**	2.41
H21 -- C3	2.13	**H21 -- C15**	2.97
C3 -- H41	2.14	**C3 -- C5**	2.38
C3 -- C6	2.77	**H31 -- C4**	2.14
C4 -- H51	2.13	**C4 -- C6**	2.41
H41 -- C5	2.14	**C5 -- H61**	2.14

Table A7 Cont.

H51 -- C6	2.13	**C7 -- H81**	2.15
C7 -- C9	2.39	**C7 -- C19**	2.77
C7 -- C11	2.40	**C7 -- H121**	2.13
C8 -- H91	2.11	**C8 -- C10**	2.37
C9 -- C11	2.75	**C8 -- C12**	2.39
H81 -- C9	2.12	**C9 -- H101**	2.13
C9 -- C11	2.37	**C9 -- C12**	2.75
H91 -- C10	2.13	**C10 -- H111**	2.12
C10 -- C12	2.39	**H101 -- C11**	2.12
C11 -- H121	2.15	**H111 -- C12**	2.15
C13 -- H141	2.15	**C13 -- H142**	2.15
C13 -- H143	2.16	**C13 -- C16**	2.53
C13 -- H161	2.74	**C13 -- C20**	2.51
C13 -- H201	2.70	**H131 -- C14**	2.15
H131 -- C15	2.08	**H131 -- C20**	2.56
C14 -- C15	2.48	**H141 -- C15**	2.68
H143 -- C15	2.76	**C15 -- H161**	2.11
C15 -- C17	2.40	**C15 -- C18**	2.81
C15 -- C19	2.44	**C15 -- H201**	2.16
C16 -- H171	2.12	**C16 -- C18**	2.38
C16 -- C19	2.74	**C16 -- C20**	2.37
H161 -- C17	2.10	**C17 -- H181**	2.15
C17 -- C19	2.39	**C17 -- C20**	2.75
H171 -- C18	2.16	**C18 -- H191**	2.12
C18 -- C20	2.39	**H181 -- C19**	2.13
C19 -- H201	2.13	**H191 -- C20**	2.14